



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 403/10, 223/16, 401/10 C07D 417/10, 227/10 C07K 5/06, C07D 281/10 A61K 31/33	A1	(11) International Publication Number: WO 92/16524 (43) International Publication Date: 1 October 1992 (01.10.92)
(21) International Application Number: PCT/US92/02271		(74) Agent: ROSE, David, L.; 126 E. Lincoln Avenue, Rahway, NJ 07065 (US).
(22) International Filing Date: 19 March 1992 (19.03.92)		(81) Designated States: BB, BG, BR, LK, MG, MN, MW, PL, RO, RU, SD.
(30) Priority data: 673,695 20 March 1991 (20.03.91) US 839,742 28 February 1992 (28.02.92) US		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
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(54) Title: BENZO-FUSED LACTAMS PROMOTE RELEASE OF GROWTH HORMONE

(57) Abstract

There are disclosed certain novel compounds identified as benzo-fused lactams which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to increase the stature of those afflicted with a lack of a normal secretion of natural growth hormone. Growth promoting compositions containing such benzo-fused lactams as the active ingredient thereof are also disclosed.

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TITLE OF THE INVENTION

BENZO-FUSED LACTAMS PROMOTE RELEASE OF GROWTH HORMONE

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CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of our copending application serial number 673695, filed 20 March 1991.

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BACKGROUND OF THE INVENTION

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Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic process of the body:

1. Increased rate of protein synthesis in all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

25

A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

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Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering an agent which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recently, recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

Other compounds have been developed which stimulate the release of endogenous growth hormone

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such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases.

5 As with most peptides, their potential for oral bioavailability is low. The instant compounds are non-peptidyl agents for promoting the release of growth hormone which may be administered

10 parenterally, nasally or by the oral route.

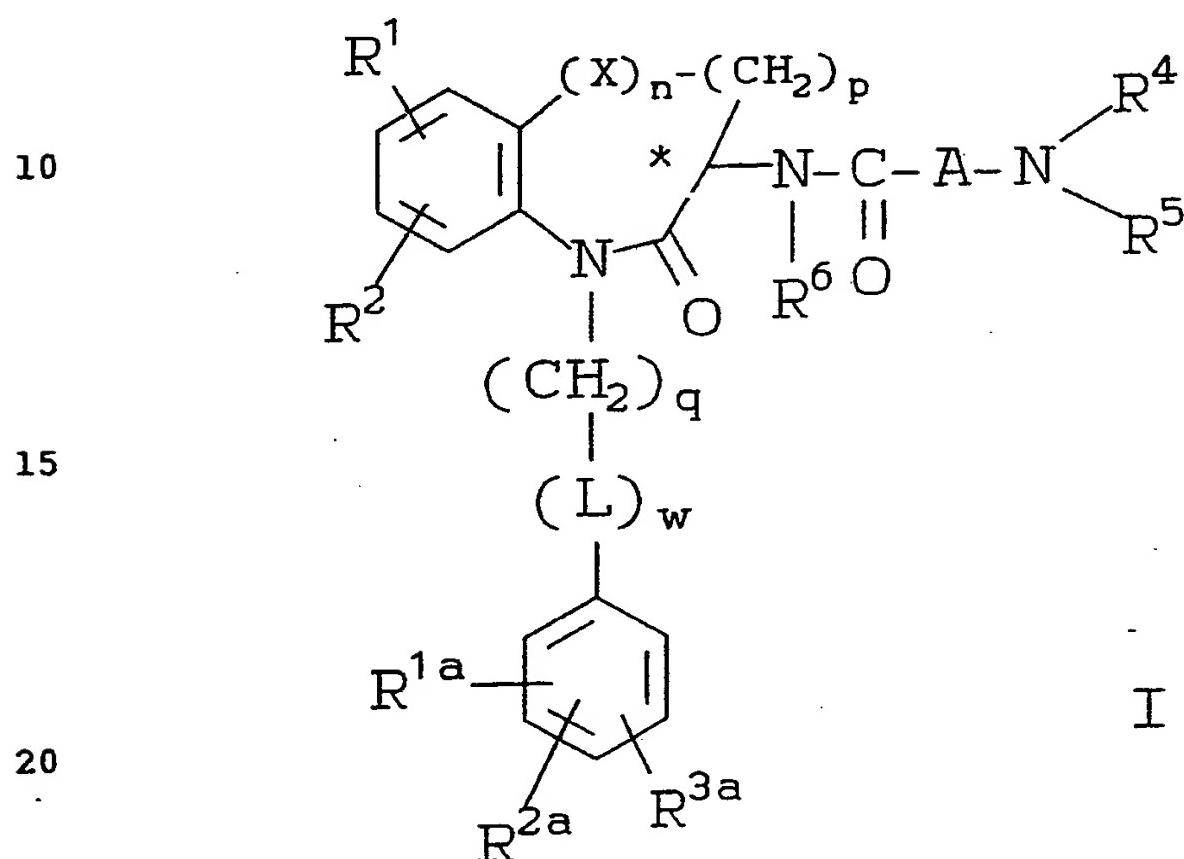
SUMMARY OF THE INVENTION

The instant invention covers certain benzo-fused lactam compounds which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the benzo-fused lactam compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the benzo-fused lactam compounds for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

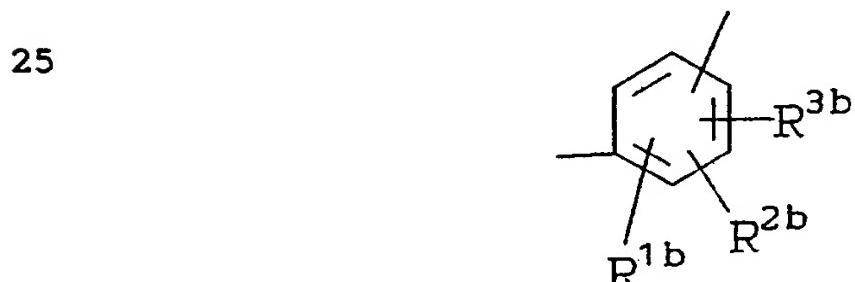
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DESCRIPTION OF THE INVENTION

The novel benzo-fused lactams of the instant invention are best described in the following structural formula I:



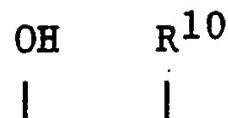
where L is



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- n is 0 or 1;
- p is 0 to 3;
- q is 0 to 4;
- w is 0 or 1;

- 5 -



X is C=O, O, S(O)_m, -CH-, -N-, -CH=CH-;

5 m is 0 to 2;

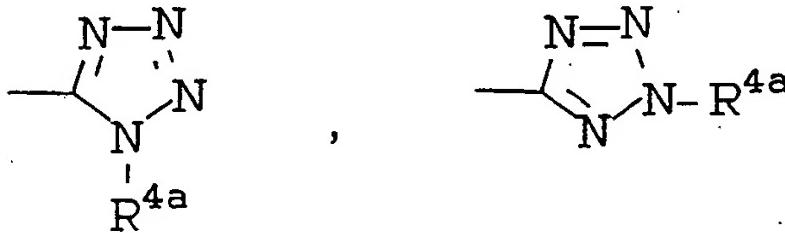
R¹, R², R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C₁-C₇ alkyl, C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy, -S(O)_mR^{7a}, cyano, nitro, R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, R^{7b}OCO(CH₂)_v, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or hydroxy;

10 R^{7a} and R^{7b} are independently hydrogen, C₁-C₃ perfluoroalkyl, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the phenyl substituents are from 1 to 3 of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or hydroxy and v is 0 to 3;

15 R^{3a} and R^{3b} are independently hydrogen, R⁹, C₁-C₆ alkyl substituted with R⁹, phenyl substituted with R⁹ or phenoxy substituted with R⁹;

20 R⁹ is

25



30

R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, R^{7b}OCO(CH₂)_v-, R^{7b}CO(CH₂)_v-, R^{7b}O(CH₂)_vCO-, R⁴R⁵N(CH₂)_v-, R^{7b}CON(R⁴)(CH₂)_v-, R⁴R⁵NCO(CH₂)_v-, R⁴R⁵NCS(CH₂)_v-, R⁴R⁵NN(R⁵)CO(CH₂)_v-, R⁴R⁵NN(R⁵)CS(CH₂)_v-, R^{7b}CON(R⁴)N(R⁵)CO(CH₂)_v-, R^{7b}CON(R⁴)N(R⁵)CS(CH₂)_v-, R⁴N(OR^{7b})CO(CH₂)_v- or R^{7a}CON(OR^{7b})CO(CH₂)_v-;

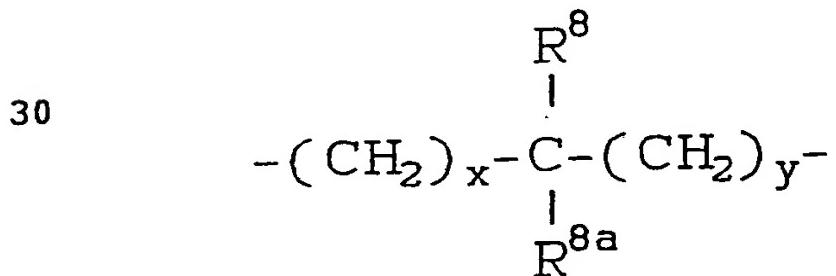
- 6 -

and v is as defined above;

R⁴, R^{4a}, R⁵ are independently hydrogen, phenyl,
 5 substituted phenyl, C₁-C₁₀ alkyl, substituted C₁-C₁₀
 alkyl, C₃-C₁₀ alkenyl, substituted C₃-C₁₀ alkenyl,
 C₃-C₁₀ alkynyl, or substituted C₃-C₁₀ alkynyl where
 the substituents on the phenyl, alkyl, alkenyl or
 alkynyl are from 1 to 5 of hydroxy, C₁-C₆ alkoxy,
 10 C₃-C₇ cycloalkyl, phenyl C₁-C₃ alkoxy, fluoro, R¹
 substituted or R¹, R² independently disubstituted
 phenyl C₁-C₃ alkoxy, phenyl, R¹ substituted or R¹, R²
 independently disubstituted phenyl, where the
 substituents on the phenyl are as defined above,
 15 C₁-C₅-alkanoyloxy, C₁-C₅ alkoxycarbonyl, carboxy,
 formyl, or -NR¹⁰R¹¹ where R¹⁰ and R¹¹ are
 independently hydrogen, C₁-C₆ alkyl, phenyl, phenyl
 C₁-C₆ alkyl, C₁-C₅-alkoxycarbonyl, or C₁-C₅-alkanoyl-
 C₁-C₆ alkyl; or R⁴ and R⁵ can be taken together to
 20 form -(CH₂)_rB(CH₂)_s- where B is CH₂, O or S(O)_m or
 N-R¹⁰, r and s are independently 1 to 3 and R¹⁰ is as
 defined above;

R⁶ is hydrogen, C₁-C₁₀ alkyl, phenyl or phenyl C₁-C₁₀
 25 alkyl;

A is



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where x and y are independently 0-3;
R⁸ and R^{8a} are independently hydrogen, C₁-C₁₀ alkyl,
trifluoromethyl, phenyl, substituted C₁-C₁₀ alkyl
5 where the substituents are from 1 to 3 of imidazolyl,
indolyl, hydroxy, fluoro, S(O)_mR^{7a}, C₁-C₆ alkoxy,
C₃-C₇ cycloalkyl, phenyl C₁-C₃ alkoxy, R¹ substituted
or R¹, R² independently disubstituted phenyl C₁-C₃
10 alkoxy, phenyl, R¹ substituted or R¹, R²
independently disubstituted phenyl,
C₁-C₅-alkanoyloxy, C₁-C₅ alkoxycarbonyl, carboxy,
formyl, or -NR¹⁰R¹¹ where R¹⁰ and R¹¹ are as defined
above; or R⁸ and R^{8a} can be taken together to form
- (CH₂)_t - where t is 2 to 6; and R⁸ and R^{8a} can
15 independently be joined to one or both of R⁴ and R⁵
to form alkyl bridges between the terminal nitrogen
and the alkyl portion of the A group wherein the
bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

20 In the above structural formula and
throughout the instant specification, the following
terms have the indicated meanings:

25 The alkyl groups specified above are
intended to include those alkyl groups of the
designated length in either a straight or branched
configuration. Exemplary of such alkyl groups are
methyl, ethyl, propyl, isopropyl, butyl, sec-butyl,
tertiary butyl, pentyl, isopentyl, hexyl, isoheptyl,
and the like.

30 The alkoxy groups specified above are
intended to include those alkoxy groups of the
designated length in either a straight or branched
configuration. Exemplary of such alkoxy groups are
methoxy, ethoxy, propoxy, isopropoxy, butoxy,

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isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

5 The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

10 Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

15 Preferred compounds of the instant invention are realized when in the above structural formula:

n is 0 or 1;
15 p is 0 to 3;
q is 0 to 2;
w is 0 or 1;

R¹⁰

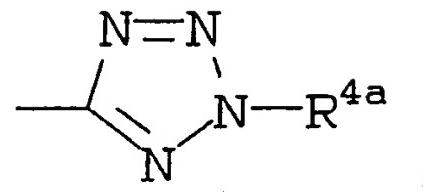
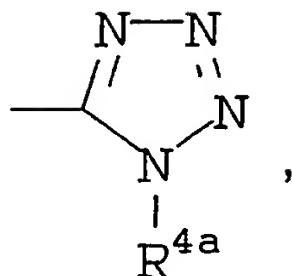
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20 X is O, S(O)_m, -N-, -CH=CH-;
m is 0 to 2;
R¹, R², R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C₁-C₇ alkyl, C₁-C₃ perfluoroalkyl, -S(O)_mR^{7a}, R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, R^{7b}OCO(CH₂)_v, phenyl or substituted phenyl where the substituents
25 are from 1 to 3 of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or hydroxy;
R^{7a} and R^{7b} are independently hydrogen, C₁-C₃ perfluoroalkyl, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, where the substituents are phenyl; phenyl and v is 0
30 to 2;
R^{3a} and R^{3b} are independently hydrogen, R⁹, C₁-C₆ alkyl substituted with R⁹, phenyl substituted with R⁹ or phenoxy substituted with R⁹;

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R⁹ is

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R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, R^{7b}OCO(CH₂)_v-, R^{7b}CO(CH₂)_v-, R⁴R⁵N(CH₂)_v-, R^{7b}CON(R⁴)(CH₂)_v-, R⁴R⁵NCO(CH₂)_v-, R⁴R⁵NCS(CH₂)_v-, R⁴R⁵NN(R⁵)CO(CH₂)_v-, R^{7b}CON(R⁴)N(R⁵)CO(CH₂)_v-, R⁴N(OR^{7b})CO(CH₂)_v- or

15

R^{7a}CON(OR^{7b})CO(CH₂)_v-; where v is as defined above; R⁴, R^{4a}, R⁵ are independently hydrogen, C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, phenyl C₁-C₃ alkoxy, fluoro, R¹ substituted or R¹, R² independently disubstituted phenyl C₁-C₃ alkoxy, phenyl, R¹ substituted or R¹, R² independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C₁-C₅-alkanoyloxy, C₁-C₅ alkoxy carbonyl, carboxy or formyl;

20

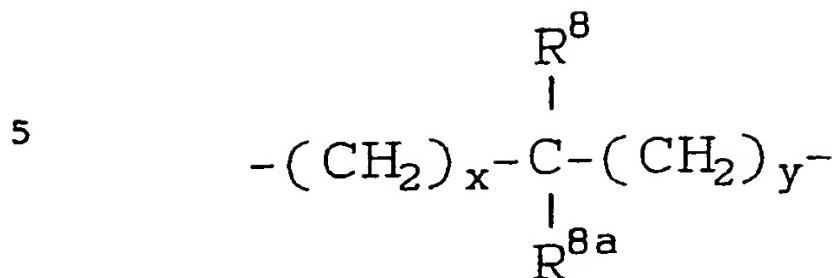
R⁴ and R⁵ can be taken together to form -(CH₂)_rB(CH₂)_s- where B is CH₂, O or S(O)_m or N-R¹⁰ r and s are independently 1 to 3 and R¹⁰ is as defined above;

25

30 R⁶ is hydrogen, C₁-C₁₀ alkyl or phenyl C₁-C₁₀ alkyl;

A is

- 10 -



10

where x and y are independently 0-2

15 R⁸ and R^{8a} are independently hydrogen, C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, S(O)_mR^{7a}, C₁-C₆ alkoxy, phenyl, R¹ substituted or R¹, R² independently disubstituted phenyl,

20 C₁-C₅-alkanoyloxy, C₁-C₅ alkoxy carbonyl, carboxy, formyl, -NR¹⁰R¹¹ where R¹⁰ and R¹¹ are independently hydrogen, C₁-C₆ alkyl, or C₁-C₅ alkanoyl-C₁-C₆ alkyl; or R⁸ and R^{8a} can be taken together to form -(CH₂)_t-where t is 2 to 4; and R⁸ and R^{8a} can independently be joined to one or both of R⁴ and R⁵ to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms;
25 and pharmaceutically acceptable salts thereof.

Additional preferred compounds are realized in the above structural formula when:
n is 0 or 1;
p is 0 to 2;
q is 0 to 2;
w is 0 or 1;

SUBSTITUTE SHEET

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X is S(0)_m, -CH=CH-;

m is 0 or 1;

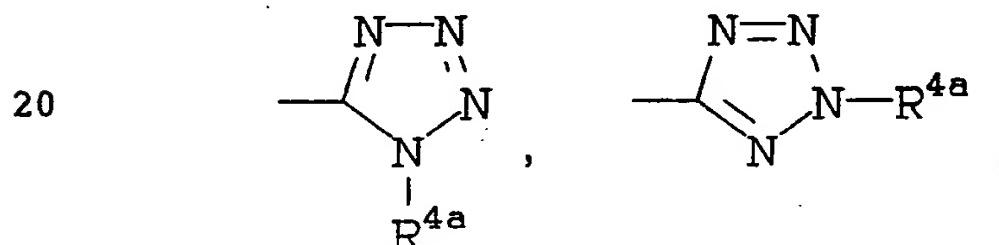
5 R¹, R², R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C₁-C₇ alkyl, C₁-C₃ perfluoroalkyl, -S(0)_mR^{7a}, R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, R^{7b}OCO(CH₂)_v, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or hydroxy;

10 R^{7a} and R^{7b} are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, where the substituents are phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R⁹, C₁-C₆ alkyl substituted with R⁹, phenyl substituted with R⁹

15 or phenoxy substituted with R⁹;

R⁹ is



25

R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, R^{7b}OCO(CH₂)_v-,
R^{7b}CO(CH₂)_v-, R⁴R⁵N(CH₂)_v-, R^{7b}CON(R⁴)(CH₂)_v-,
R⁴R⁵NCO(CH₂)_v-, R⁴R⁵NCS(CH₂)_v-, R⁴N(OR^{7b})CO(CH₂)_v- or
R^{7a}CON(OR^{7b})CO(CH₂)_v-; where v is as defined above;

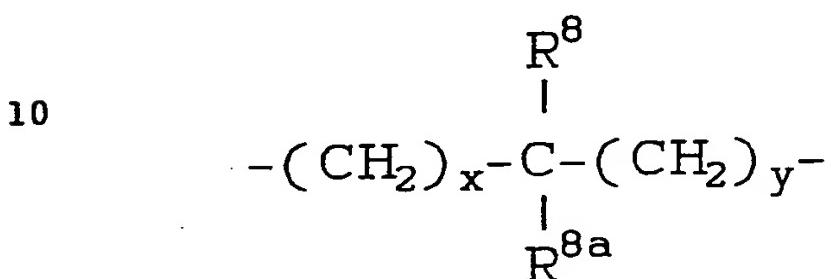
30 R⁴, R^{4a}, R⁵ are independently hydrogen, C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C₁-C₆ alkoxy, fluoro, phenyl, R¹ substituted or R¹, R² independently disubstituted phenyl, where

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the substituents on the phenyl are as defined above,
 C_1-C_5 -alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy;

5 R^6 is hydrogen, C_1-C_{10} alkyl;

A is



15 where x and y are independently 0-2;
 R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl,
 substituted C_1-C_{10} alkyl where the substituents are
 from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro,
 $S(O)_{m}R^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1 ,
 R^2 independently disubstituted phenyl,
 20 C_1-C_5 -alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy; or
 R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$
 where t is 2; and R^8 and R^{8a} can independently be
 joined to one or both of R^4 and R^5 to form alkyl
 bridges between the terminal nitrogen and the alkyl
 25 portion of the A group wherein the bridge contains
 from 1 to 5 carbon atoms;
 and pharmaceutically acceptable salts thereof.

30 Still further preferred compounds of the
 instant invention are realized in the above
 structural formula when;
 n is 0 or 1;
 p is 0 to 2;

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q is 1;

w is 1;

X is S(0)_m, -CH=CH-;

5 m is 0 or 1;

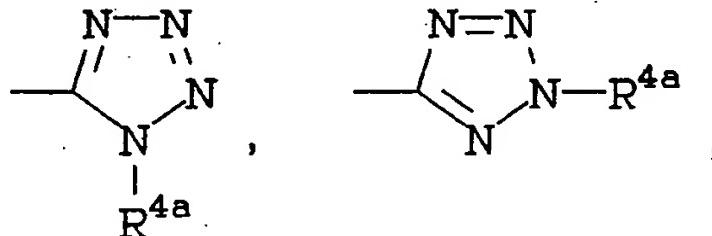
R¹, R², R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C₁-C₇ alkyl, C₁-C₃ perfluoroalkyl, -S(0)_mR^{7a}, R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or hydroxy;

10 R^{7a} and R^{7b} are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, where the substituents are phenyl, phenyl and v is 0 or 1;

15 R^{3a} and R^{3b} are independently hydrogen or R⁹;

R⁹ is

20



25

R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, R^{7b}OCO(CH₂)_v-, R^{7b}CO(CH₂)_v-, R⁴R⁵N(CH₂)_v-, R^{7b}CON(R⁴)(CH₂)_v-, R⁴R⁵NCO(CH₂)_v- or R⁴N(OR^{7b})CO(CH₂)_v-; where v is as defined above;

30

R⁴, R⁵ are independently hydrogen, C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkyl, where the substituents on the alkyl are from 1 to 3 of hydroxy, C₁-C₃ alkoxy, fluoro, phenyl, R¹ substituted or R¹, R² independently disubstituted phenyl, where the substituents on the phenyl are as defined above;

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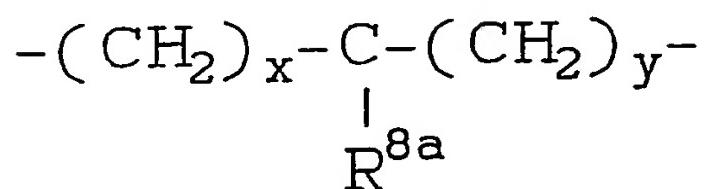
R^{4a} is hydrogen, C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkyl where the substituents on the alkyl are from 1 to 3 of hydroxy;

5

R⁶ is hydrogen;

A is

10



15

where x and y are independently 0-1;

R⁸ and R^{8a} are independently hydrogen, C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, S(O)_mR^{7a}, C₁-C₆ alkoxy, phenyl, R¹ substituted or R¹, R² independently disubstituted phenyl, C₁-C₅-alkanoyloxy, C₁-C₅ alkoxycarbonyl, carboxy; or R⁸ and R^{8a} can be taken together to form -(CH₂)_t- where t is 2; and R⁸ and R^{8a} can independently be joined to one or both of R⁴ and R⁵ to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the bridge contains from 1 to 5 carbon atoms; and pharmaceutically acceptable salts thereof.

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Representative preferred growth hormone releasing compounds of the present invention include the following:

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1. 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

10

2. 2(R)-amino-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-
1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

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3. 2(R)-amino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-
1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

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4. 2(R)-amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-
(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-
1-benzazepin-3(R)-yl]-propanamide

25

5. 3-(2-hydroxyethyl)amino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1-(2-hydroxyethyl)-tetra-
zol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benz-
azepin-3(R)-yl]-butanamide

30

6. 3-(2-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-
butanamide

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7. 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-y1]-propanamide
5
8. 3-amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-
2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide
10
9. 3-amino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-
butanamide
15
10. 3-amino-3-methyl-N-[6-fluoro-2,3,4,5-tetrahydro-
2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide
11. 3-benzylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-
oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide
20
12. 3-amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2'-(
1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1,5-benzothiazepin-3(S)-y1]-butanamide
25
13. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-
butanamide
30

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14. 3-(2(S)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
5
15. 3-(2(R),3-dihydroxypropyl)amino-3-methyl-N-[2,3,-4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
10
16. 3-(2(S),3-dihydroxypropyl)amino-3-methyl-N-[2,3,-4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide
15
17. 3-(3(S)-hydroxybutyl)amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
20
18. 3-(3(S)-hydroxybutyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
25
19. 3-amino-3-methyl-N-[7-hydroxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
30

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20. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-hydroxy-
2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-
y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-
5 3(R)-y1]-butanamide
21. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-fluoro-
2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-
y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-
10 3(R)-y1]-butanamide
22. 2-(3(R)-hydroxybutyl)amino-2-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-
biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-y1]-
15 propanamide
23. 2-(3(S)-hydroxybutyl)amino-2-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-
biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-y1]-
20 propanamide
24. 3-Amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-
2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide
25
25. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methoxy-
2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-
y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-
3(R)-y1]-butanamide
- 30

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26. 3-(3(S)-hydroxybutyl)amino-3-methyl-N-[7-methoxy-
2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)
[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-
yl]butanamide
5
27. Quinuclidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-3-carboxamide
10
28. 3-(2-fluoropropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
15
29. 3-(2-methoxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
20
30. 3-(2-hydroxy-2-methylpropyl)amino-3-methyl-N-[2,-
3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-
[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-
yl]butanamide
25
31. 4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,-
3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-
methyl]-[1,1'-biphenyl]-2-carboxamide
30
32. 4'-[[3(R)-[[3-[(2(R)-hydroxypropyl)amino]-3-
methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-
1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-
carboxamide

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33. 4'-[3(R)-[(3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide
5
34. N-ethyl-4'-[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide
10
35. N-ethyl-4'-[3(R)-[(3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide
15
36. N-methyl-4'-[3(R)-[(3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide
20
37. 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
25
38. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
30
39. 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-aminomethyl[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide

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40. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,-
5-tetrahydro-2-oxo-1-[[2'-aminomethyl[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-
butanamide
5
41. 4'-[[3(R)-[[3-[(2(S),3(S),4-trihydroxybutyl)-
amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-
hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-
biphenyl]-2-carboxamide
10
42. 4'-[[3(R)-[[3-[(3-hydroxybutyl)amino]-3-methyl-1-
oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-ben-
zazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide
15
43. 3-Amino-3-methyl-N-[2,3-dihydro-2-oxo-1-[[2'-(1H-
tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-
benzazepin-3(R)-yl]butanamide
44. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3-di-
hydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-
butanamide
20
45. N-ethyl-4'-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-
amino]-3-methyl-1-oxobutyl]amino]-2,3-dihydro-2-
oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-
2-carboxamide
25
46. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[3,4-di-
hydro-4-oxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-
y1]-butanamide
30

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47. 3-(2(S)-hydroxypropyl)amino-3-methyl-N-[3,4-di-
hydro-4-oxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-
5 yl]-butanamide
48. N-ethyl-4'-[[3(S)-[3-[(2(S),3-dihydroxypropyl)-
amino]-3-methyl-1-oxobutyl]amino]-3,4-dihydro-4-
10 oxo-1,5-benzothiazepin-5(2H)-yl]methyl]-[1,1'-bi-
phenyl]-2-carboxamide
49. 4'-[[3(S)-[(3-amino-3-methyl-1-oxobutyl)amino]-
3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2H)-yl]-
15 methyl]-[1,1'-biphenyl]-2-carboxamide
50. 4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-
2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-
methyl]-[1,1'-biphenyl]-2-thioamide
51. N-hydroxy-4'-[[3(R)-[(3-amino-3-methyl-1-oxo-
butyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-
benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-
20 carboxamide
52. N-hydroxy-4'-[[3(R)-[3-[(2(S),3-dihydroxypropyl)-
amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-
25 hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-
biphenyl]-2-carboxamide
53. N-hydroxy-4'-[[3(R)-[3-[(2(R)-hydroxypropyl)-
amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-
30 hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-
biphenyl]-2-carboxamide

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54. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide
- 5
55. 3-amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide
- 10
56. 3-amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
- 15
57. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
- 20
58. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
- 25
59. 3-amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
- 30
60. 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(acetylaminomethyl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide

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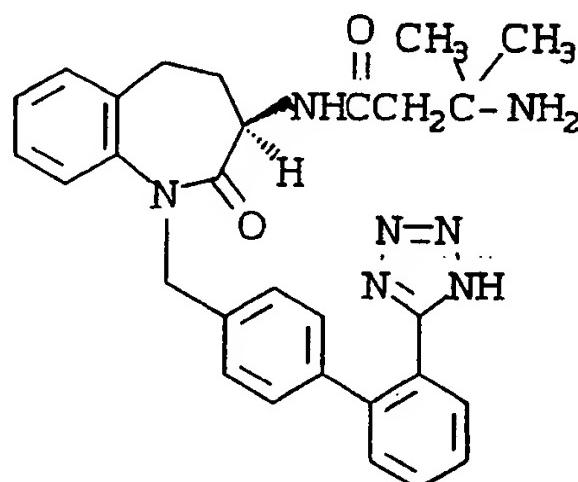
61. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(acetylaminomethyl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
5
62. 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(benzoylaminomethyl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
10
63. 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(benzoylaminomethyl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
15
64. 3-amino-3-methyl-4-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
20
65. 2-amino-2-methyl-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]propanamide
25
66. 3-(2(R)-hydroxypropyl)amino-3-methyl-4-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide
30
67. 2-(3-hydroxybutyl)amino-2-methyl-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]propanamide

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Representative examples of the nomenclature employed are given below:

5 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]butanamide

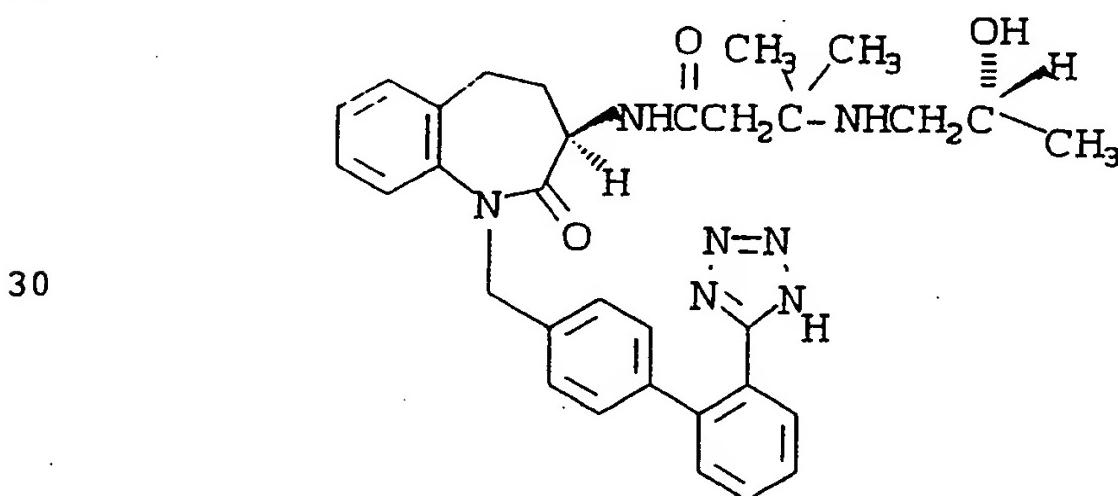
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20 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]butanamide

25

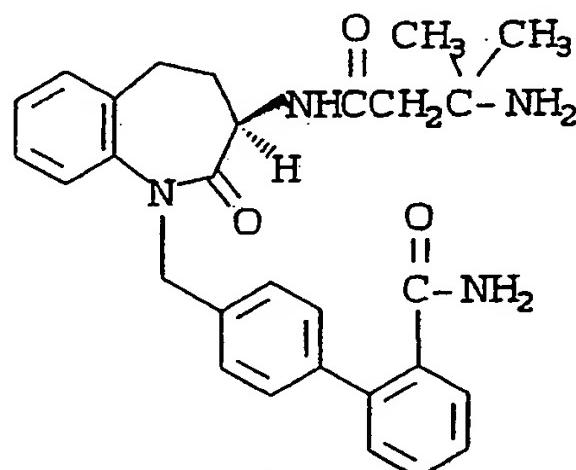


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4'-[[(3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,-
4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl)methyl]-
[1,1'-biphenyl]-2-carboxamide

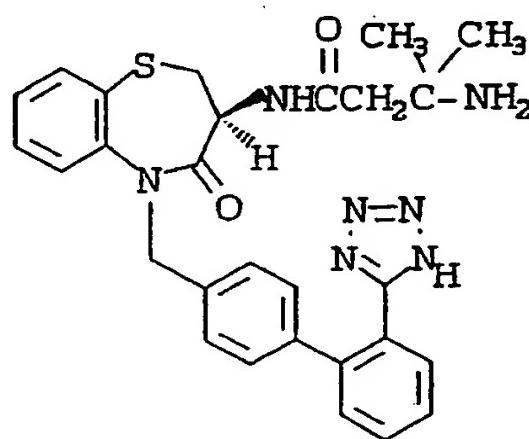
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10

3-amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]butanamide

20



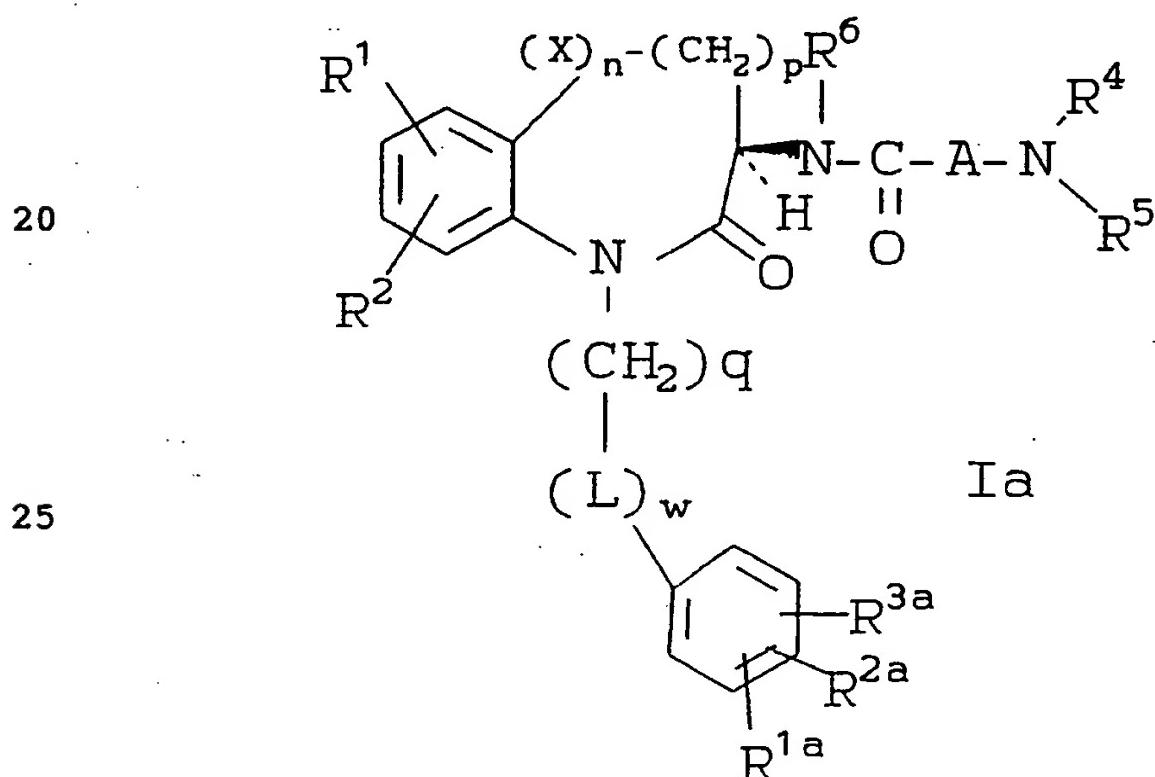
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The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I above.
Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is

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intended that all such optical isomers, as separated, pure optical isomers or racemic mixtures thereof, be included within the ambit of the instant invention.

In the case of the asymmetric center represented by the asterisk in Formula I, it has been found that the compound in which the 3-amino substituent is above the plane of the structure, as seen in Formula Ia, is more active and thus more preferred over the compound in which the 3-amino substituent is below the plane of the structure. In the substituent $(X)_n$, when $n = 0$, the asymmetric center is designated as the R-isomer. When $n = 1$, this center will be designated according to the R/S rules as either R or S depending upon the value of X.



30

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids

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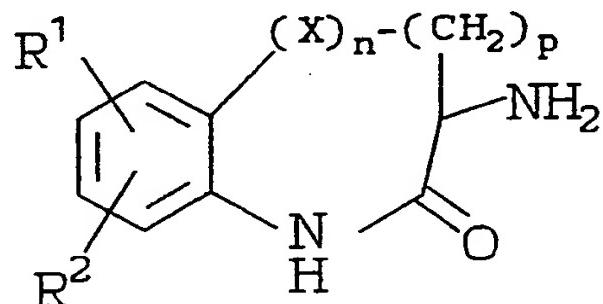
are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function such as a carboxy or tetrazole, can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

10

The compounds (I) of the present invention are prepared from aminolactam intermediates such as those of formula II. The preparation of these intermediates is described in the following reaction Schemes.

15

20



II

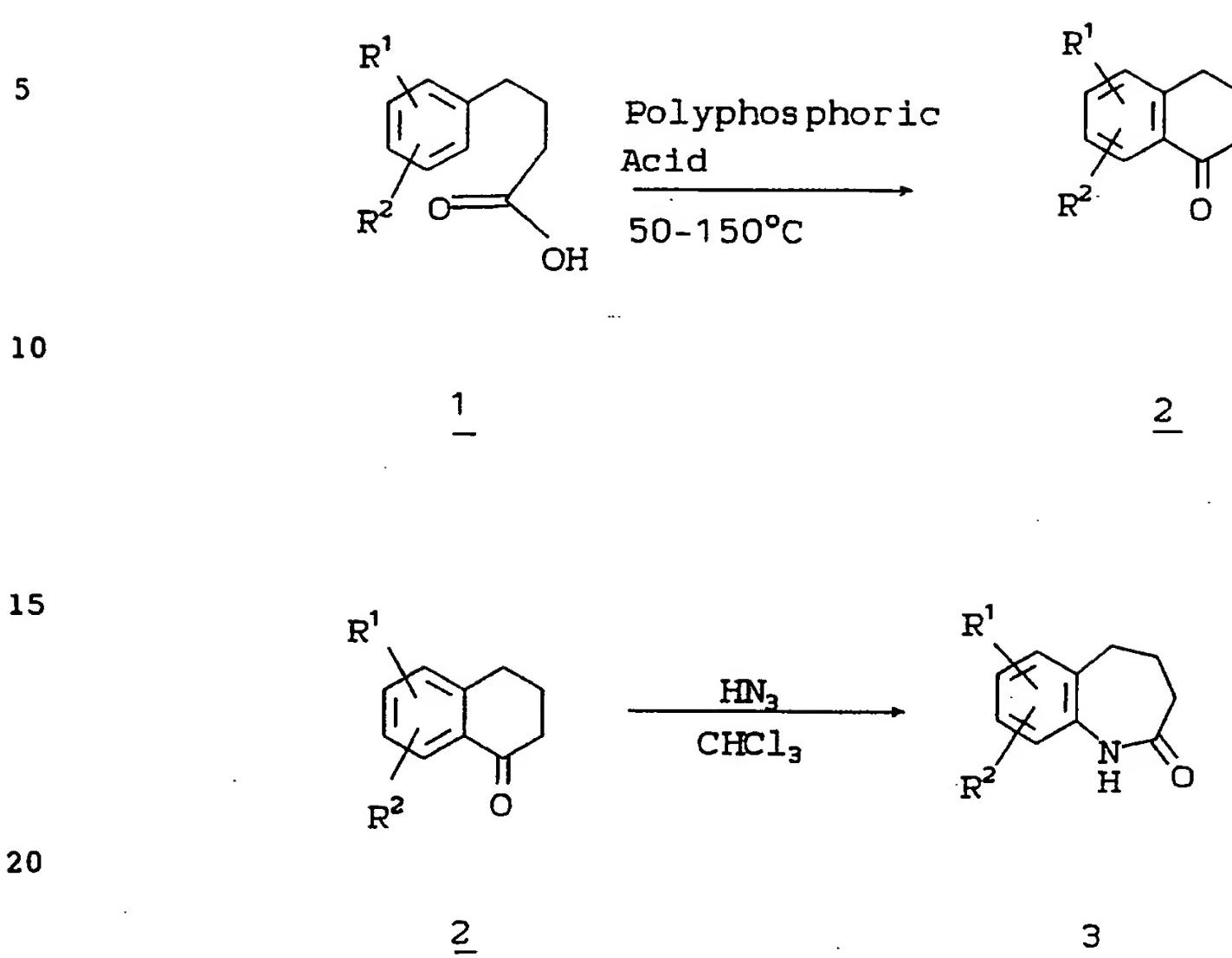
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Benzo-fused lactams 3 wherein the lactam is a seven-membered ring are conveniently prepared from substituted tetralones 2 using known procedures. The substituted tetralones are, in some cases, commercially available or are prepared from a suitably substituted derivative of 4-phenylbutyric acid 1. Cyclization of 1 can be achieved by a number of methods well known in the literature including treatment with polyphosphoric acid at elevated temperatures as shown in Scheme 1.

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Scheme 1



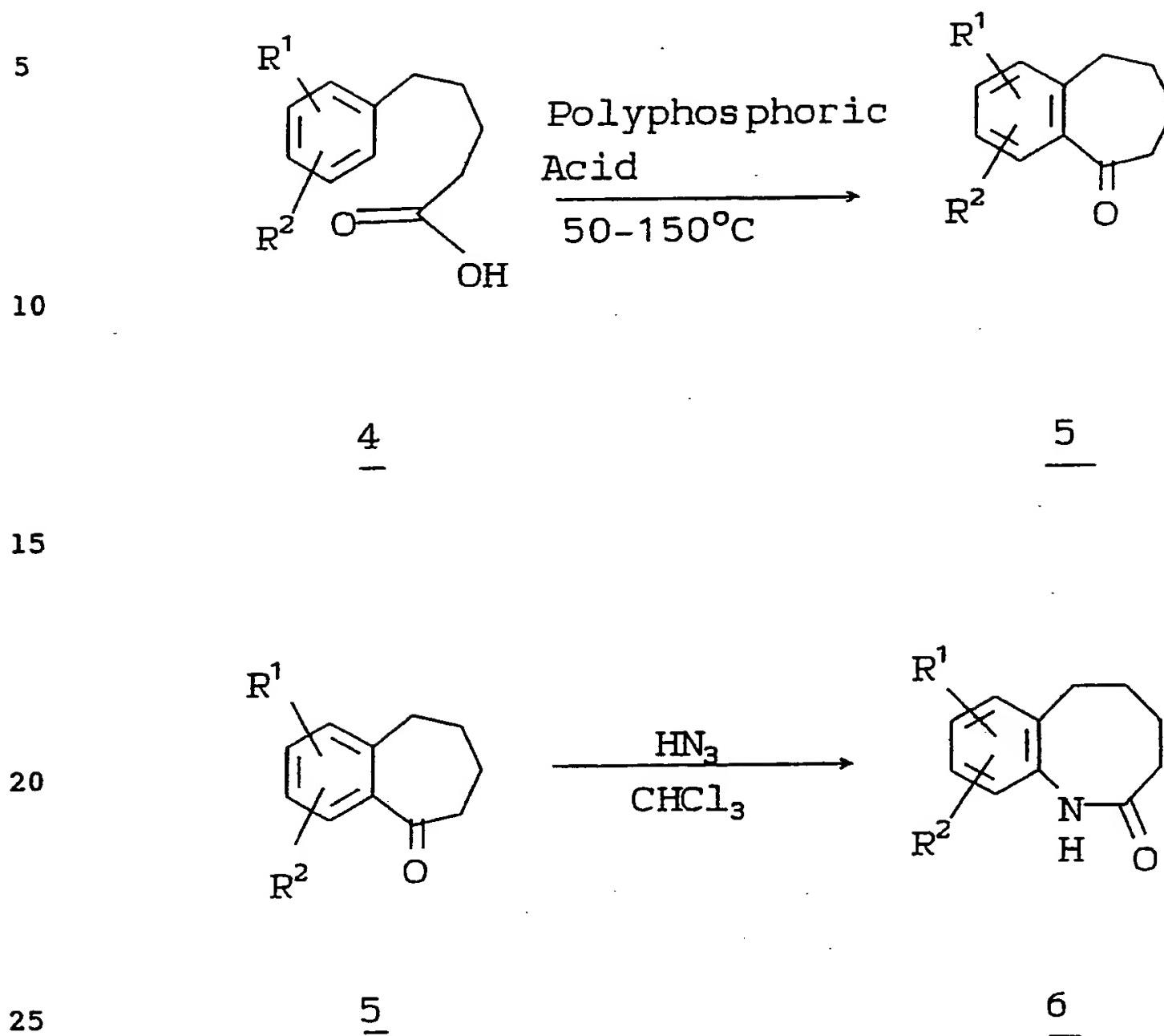
Conversion of substituted tetralones 2 to benzolactams 3 can be achieved by a number of methods familiar to those skilled in the art. A suitable method involves the use of hydrazoic acid (Schmidt reaction) to form the substituted benzolactam 3.

30 Benzo-fused lactams wherein the lactam is an
eight-membered ring (6) are prepared as described by
D. H. Jones, et al, J. Chem. Soc. C, 2176-2181 (1969)
by an analogous series of transformations starting
from a substituted derivative of 5-phenylpentanoic
acid 4 as shown in Scheme 2.

SUBSTITUTE SHEET

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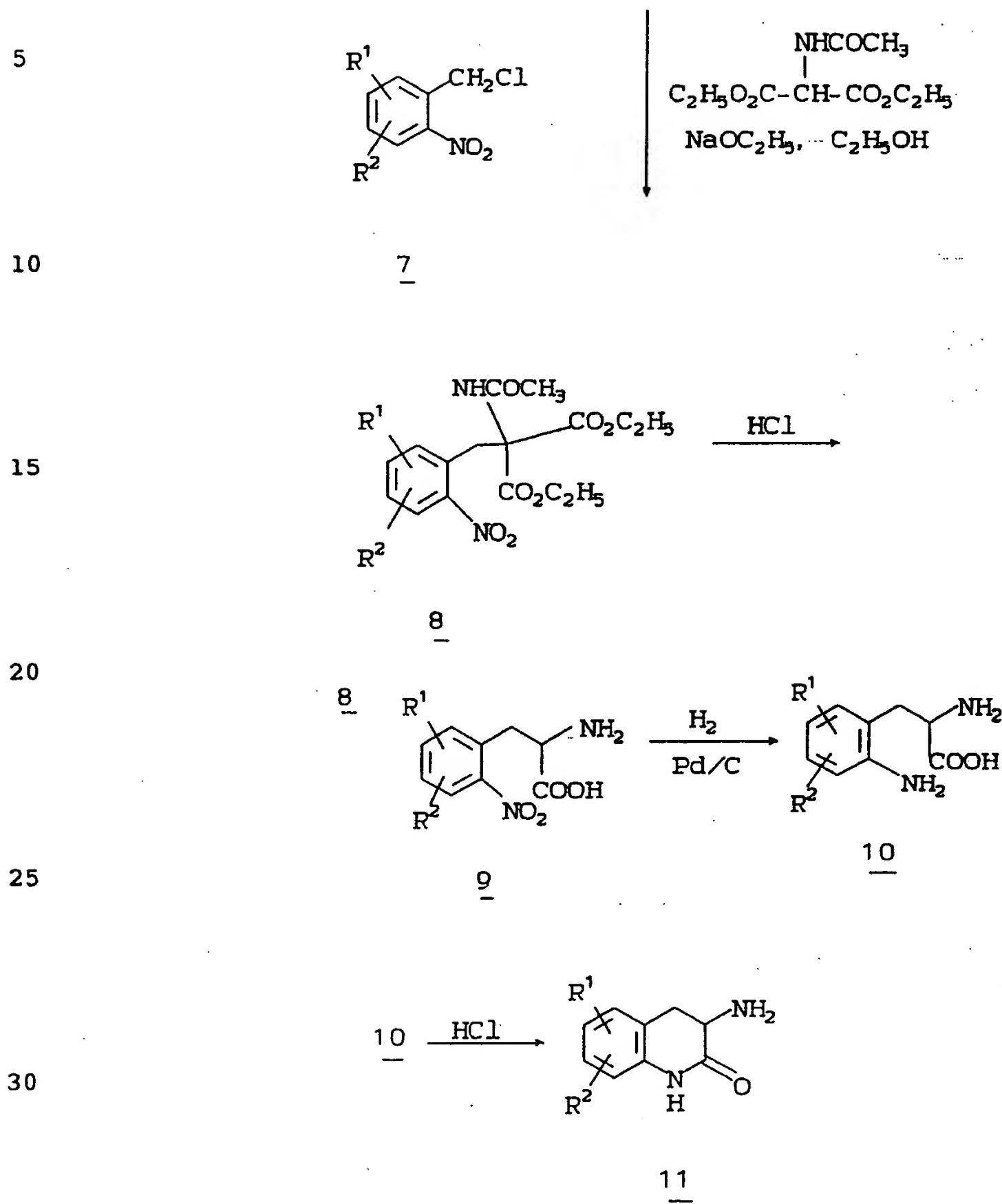
Scheme 2



As shown in Scheme 3, 3-aminobenzolactam
analog 30 wherein the lactam is a six-membered ring
(11) are prepared from a substituted derivative of
2-nitrobenzyl chloride (or bromide) 7 by the method
of A. L. Davis, et al, Arch. Biochem. Biophys., 102,
48-51 (1963) and references cited therein.

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Scheme 3



SUBSTITUTE SHEET

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Conversion of substituted benzo-fused lactams to the requisite 3-amino derivatives can be achieved by a number of methods familiar to those skilled in the art, including those described by Watthey, et al, J. Med. Chem., 28, 1511-1516 (1985) and references cited therein. One common route proceeds via the intermediacy of a 3-halo (chloro, bromo or iodo) intermediate which is subsequently displaced by a nitrogen nucleophile, typically azide. A useful method of forming the 3-iodobenzolactam intermediates 12 involves treating the benzolactam with two equivalents each of iodotrimethylsilane and iodine at low temperature, as illustrated in Scheme 4 for the seven-membered ring analogs 3.

20

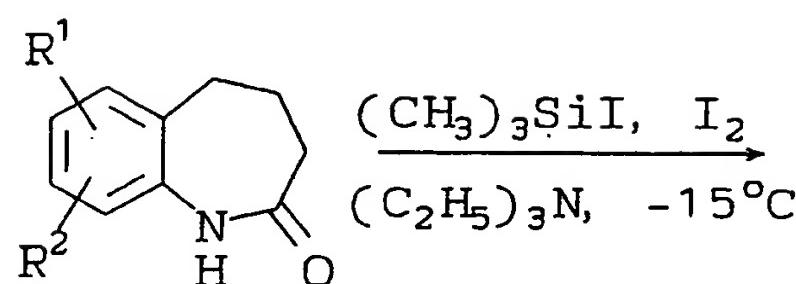
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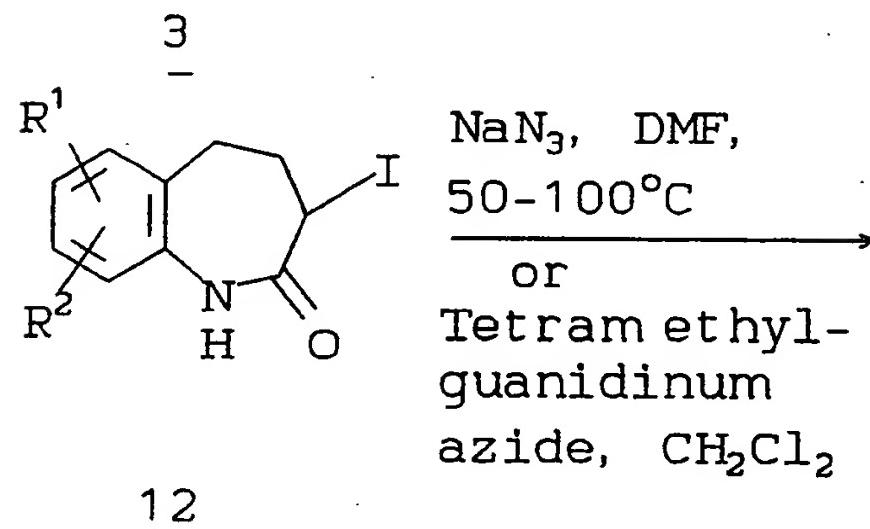
Scheme 4

5



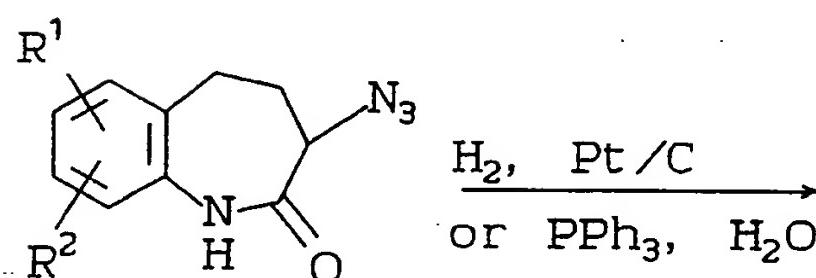
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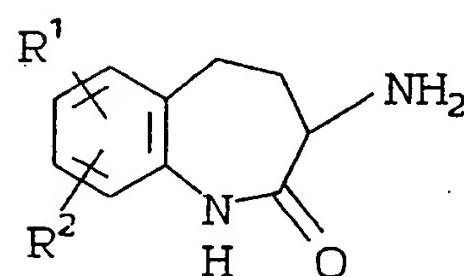


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Elaboration of the iodo-benzolactams to the desired aminolactam intermediates II is achieved by a two-step procedure illustrated in Scheme 4.

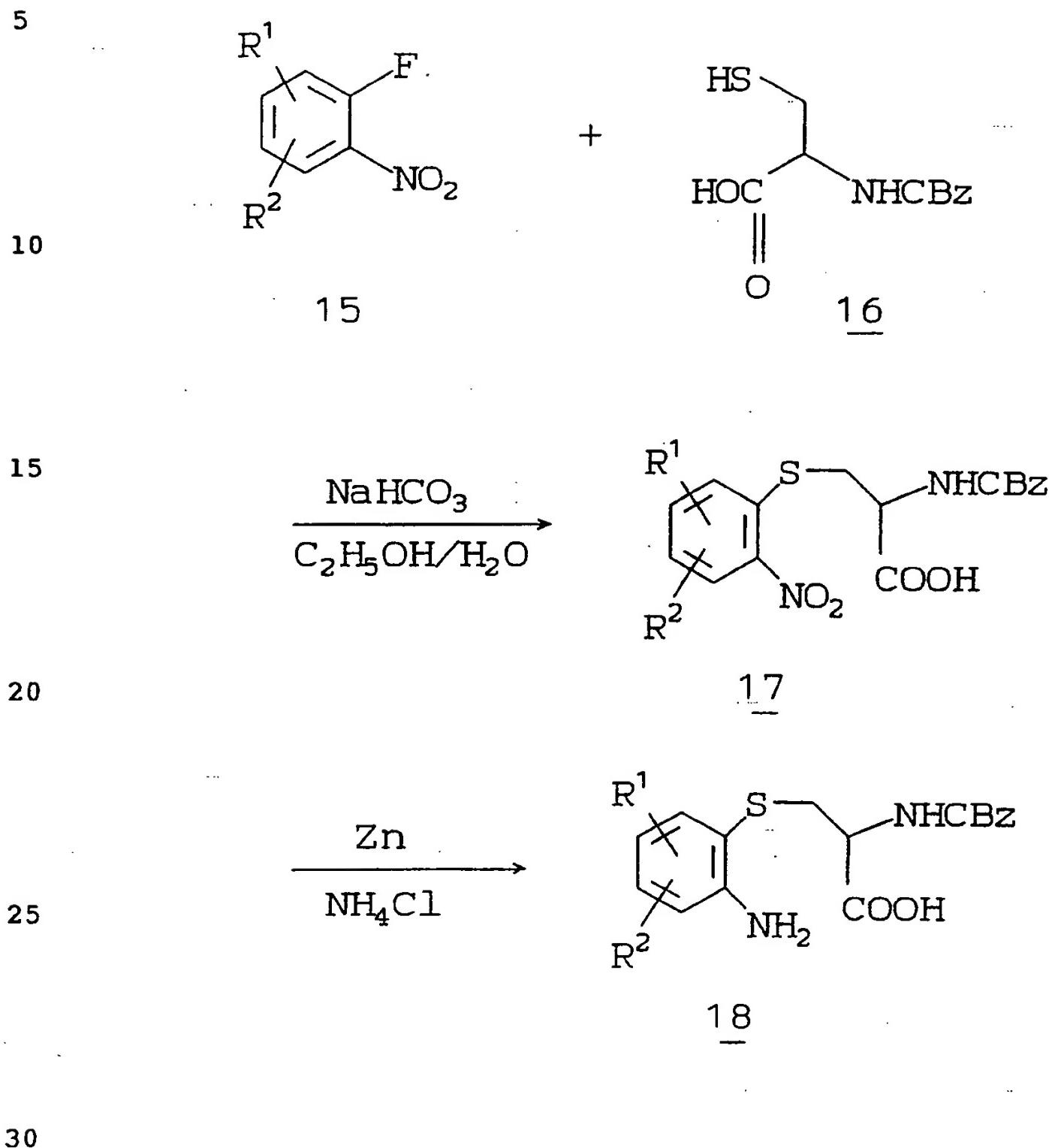
5 Typically, iodo-benzolactams 12 are treated with sodium azide in N,N-dimethylformamide at 50-100°C to give the 3-azido derivatives 13. Alternatively, tetramethylguanidinium azide in a solvent such as methylene chloride can be employed to achieve similar 10 results. Hydrogenation with a metal catalyst, such as platinum on carbon, or alternatively, treatment with triphenylphosphine in wet toluene, results in formation of the amine derivative 14. Formation of the analogous derivatives of the eight-membered 15 benzolactams is also achieved by the routes shown in Scheme 4.

Chiral aminobenzolactams are obtained by resolution of the racemates by classical methods familiar to those skilled in the art. For example, 20 resolution can be achieved by formation of diastereomeric salts of the racemic amines with optically active acids such as D- and L-tartaric acid. Determination of absolute stereochemistry can be achieved in a number of ways including X-ray 25 analysis of a suitable crystalline derivative.

Intermediates of Formula II wherein X is a sulfur atom are prepared by methods described in the literature and known to those skilled in the art. As 30 illustrated in Scheme 5, the seven-membered ring analog 22 is prepared from a protected derivative of cysteine 16 by the method of Slade, et al, J. Med. Chem., 28, 1517-1521 (1985) and references cited therein (Cbz = benzyloxycarbonyl).

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Scheme 5

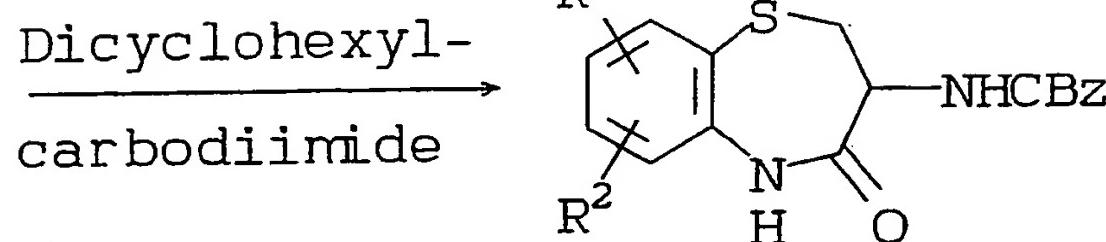


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Scheme 5 (Con't)

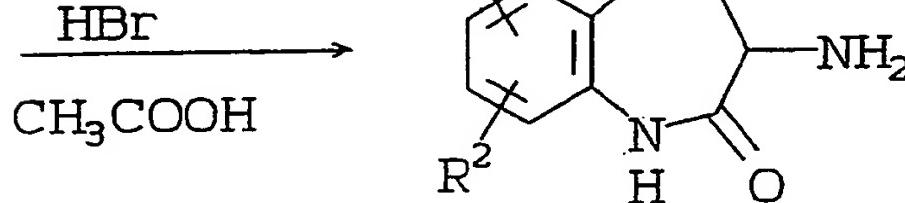
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19 r = 0, 20 r = 1, 21 r = 2

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22 r = 0, 23 r = 1, 24 r = 2

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Sulfoxide and sulfone intermediates 23 and 24 are prepared by oxidation of 19 with various oxidants such as sodium periodate or meta-chloroperbenzoic acid. Eight-membered ring intermediates of Formula II wherein X is sulfur can be prepared by an analogous route starting from derivatives of homo-cysteine.

30

Intermediates of Formula II wherein X is an oxygen atom are prepared by methods described in the literature and known to those skilled in the art.

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For example, the seven-membered ring analog 26 can be prepared from a substituted derivative of 3-(2-nitro-phenoxy)butyric acid 25 by the method of J. Ott,
5 Arch. Pharm. (Weinheim, Ger.), 323(9), 601-603 (1990).

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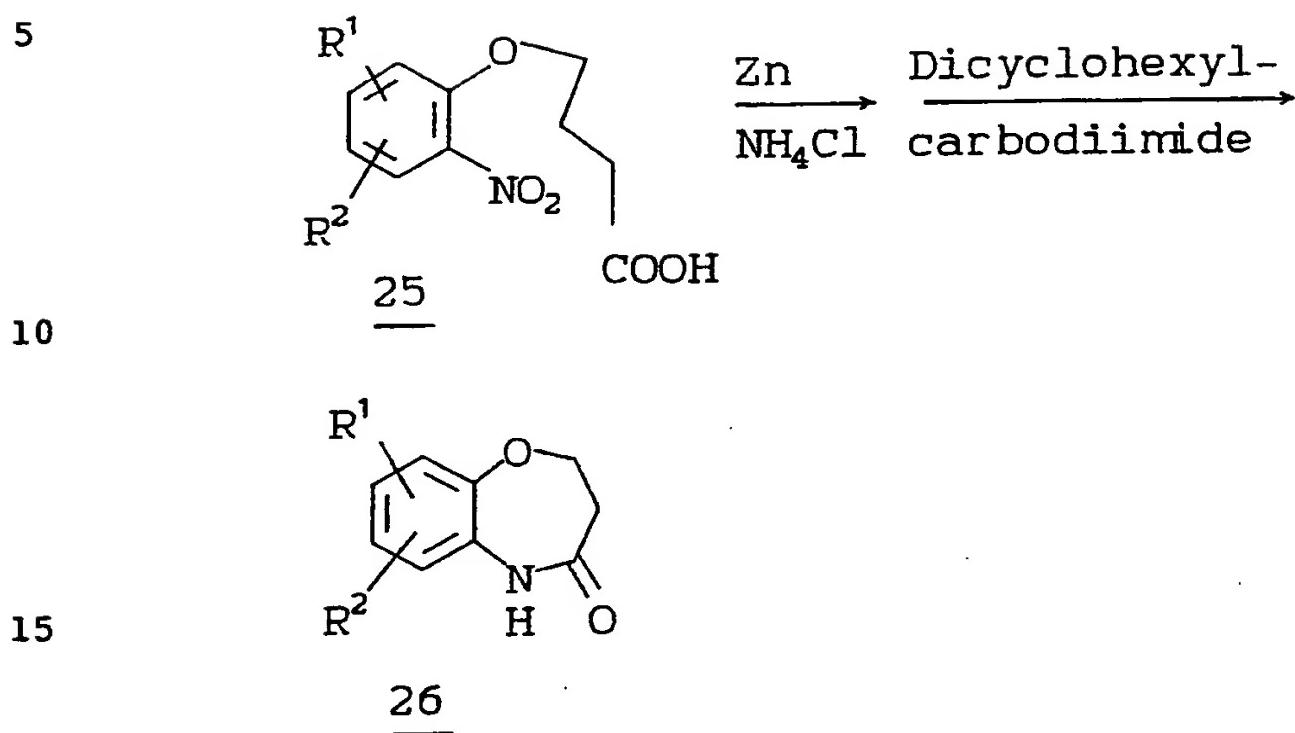
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- 37 -

Scheme 6



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Six-membered ring analogs wherein X is oxygen (28) may be prepared by reaction of a substituted derivative of 2-aminophenol 27 with chloroacetyl chloride by the method of Huang and Chan, *Synthesis*, 10, 851 (1984) and references cited therein. Subsequent incorporation of an amino group at the 3 position of either 26 or 28 is achieved by the methods described in Scheme 4.

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Scheme 7

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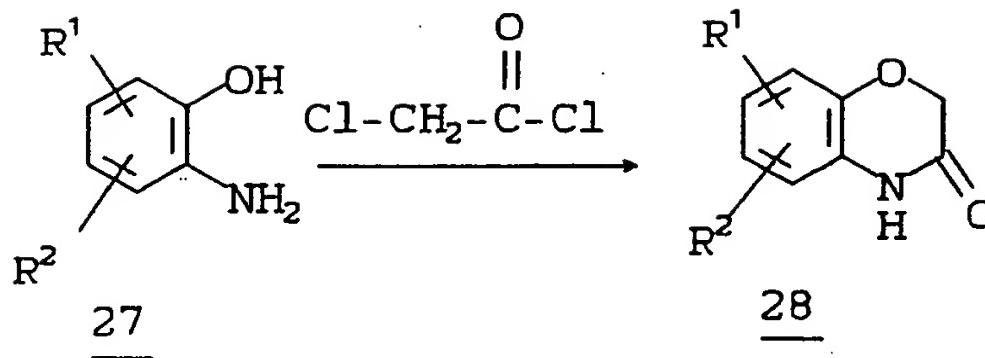
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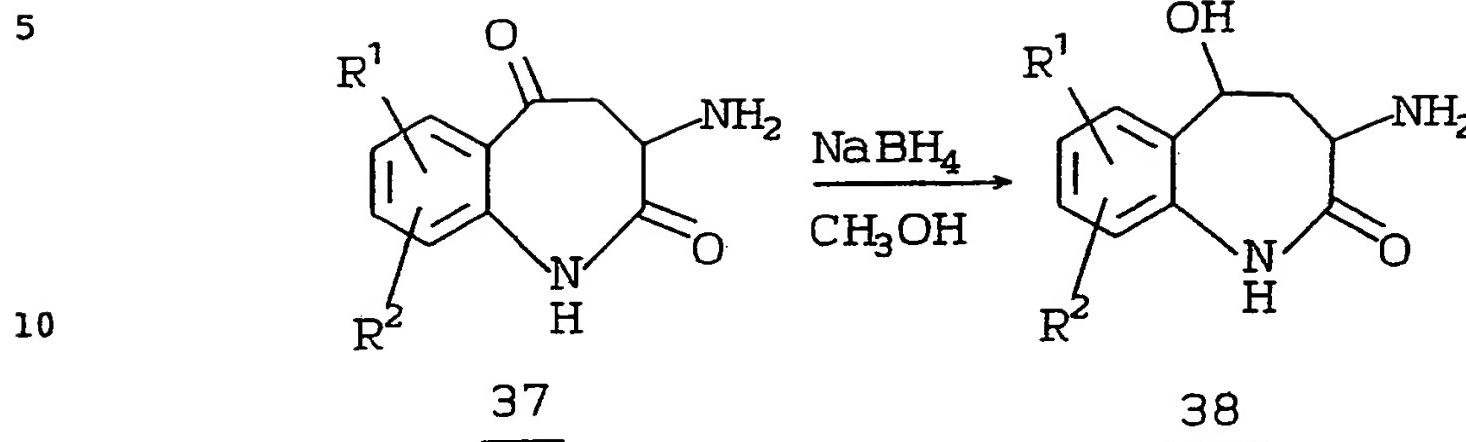
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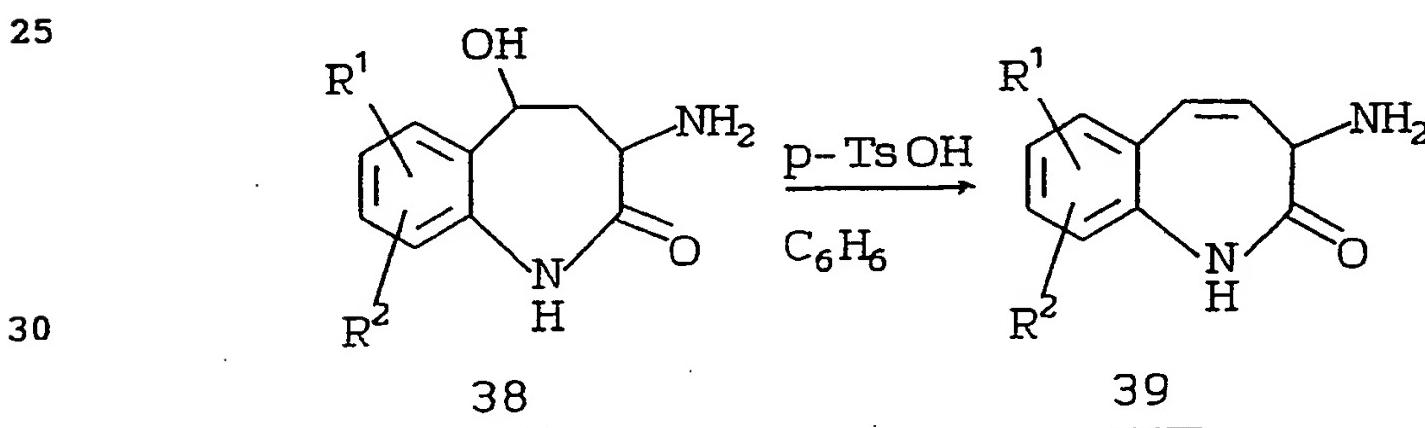
Seven-membered ring analogs of Formula II wherein X is C=O can be prepared from derivatives of tryptophan as described in the Australian Journal of Chemistry, 33, 633-640 (1980). Seven-membered ring analogs of Formula II wherein X is CH=CH can be prepared from the aforementioned analogs wherein X is C=O. Treatment of 37 with chemical reducing agents such as sodium borohydride in a polar solvent such as methanol or ethanol results in reduction to give the secondary alcohol derivative 38 (X=CHOH).

- 39 -



15 Dehydration of 38 can be achieved by several methods described in the literature and familiar to those skilled in the art. For example, treatment of 38 in an inert solvent, such as benzene, with a strong acid such as p-toluenesulfonic acid, will result in dehydration to the unsaturated analog 39.

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- 39/1 -

Intermediates of formula II can be further elaborated to new intermediates (formula III) which are substituted on the amino group (Scheme 8).

5 Reductive alkylation of II with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in

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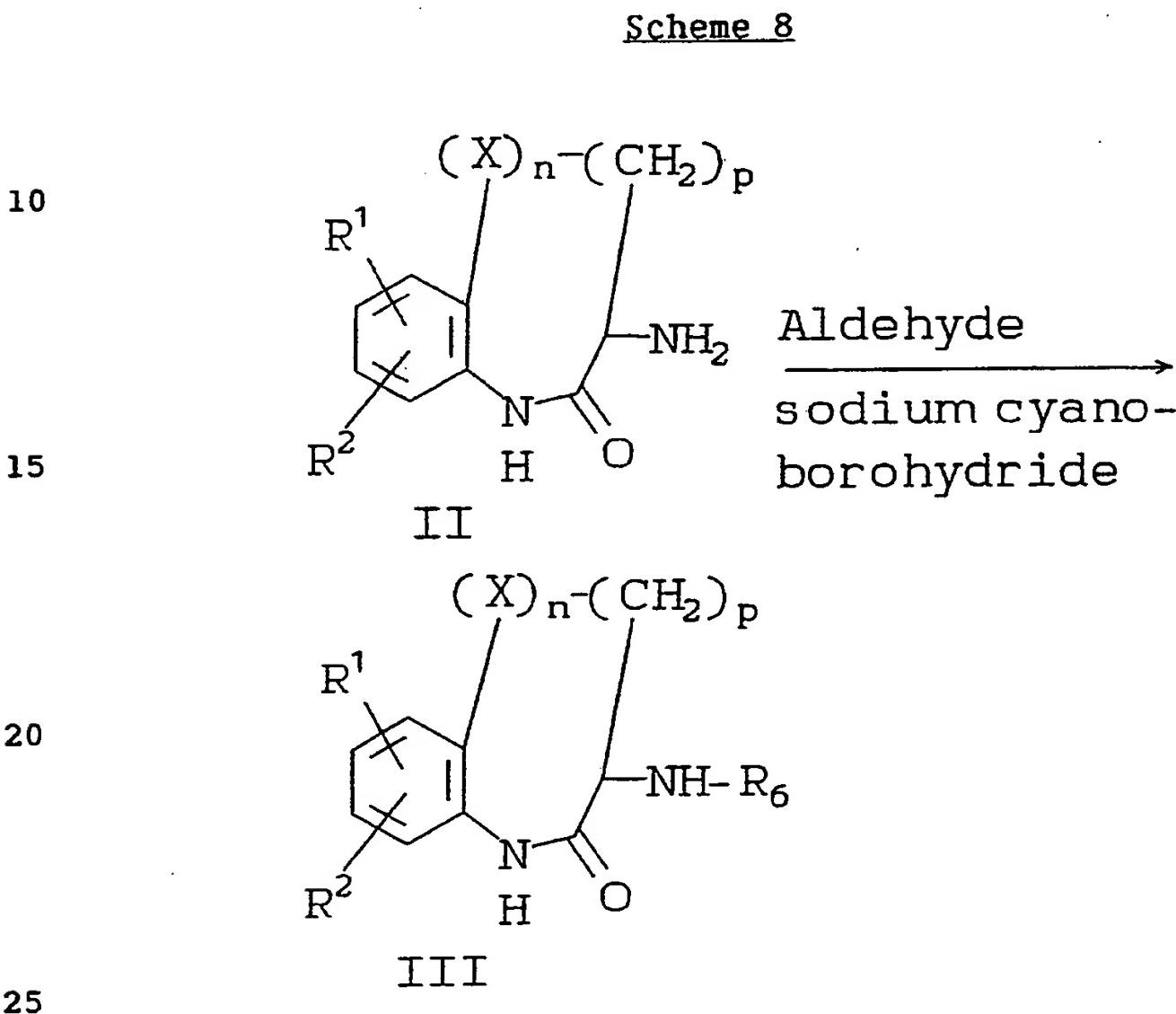
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- 40 -

the presence of platinum, palladium or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in an inert solvent such as methanol or ethanol.



Attachment of the amino acid sidechain to intermediates of formula III is accomplished by the route shown in Scheme 9. Coupling is conveniently carried out by the use of an appropriately protected amino acid derivative, such as that illustrated by formula IV, and a coupling reagent such as

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benzotriazol-1-yloxytris(dimethylamino)phosphonium
hexafluorophosphate ("BOP") in an inert solvent such
as methylene chloride. Separation of unwanted side
products, and purification of intermediates is
achieved by chromatography on silica gel, employing
flash chromatography (W.C. Still, M. Kahn and A.

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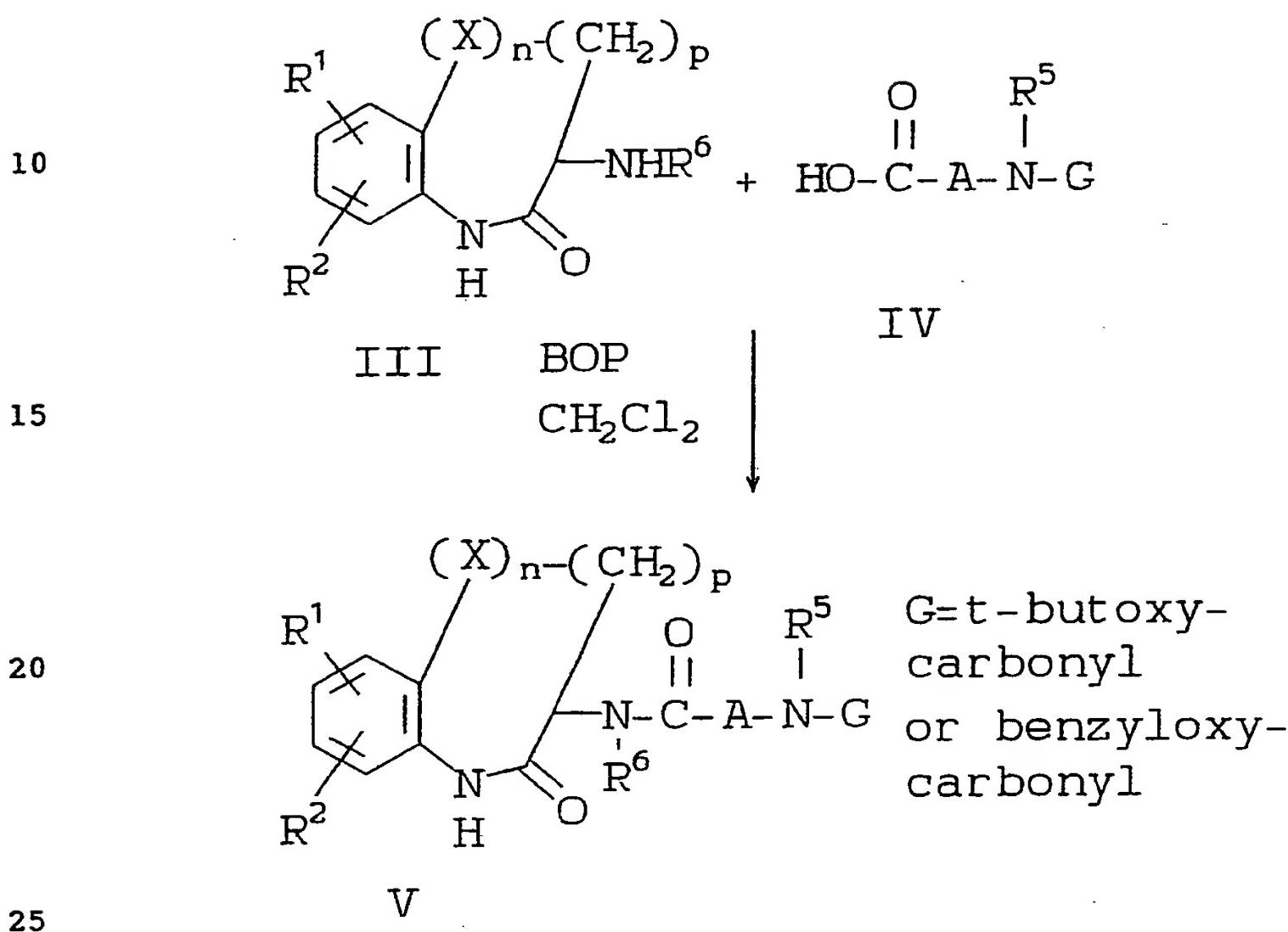
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- 41 -

Mitra, J. Org. Chem., 43, 2923 (1978)) or by medium pressure liquid chromatography.

5

Scheme 9

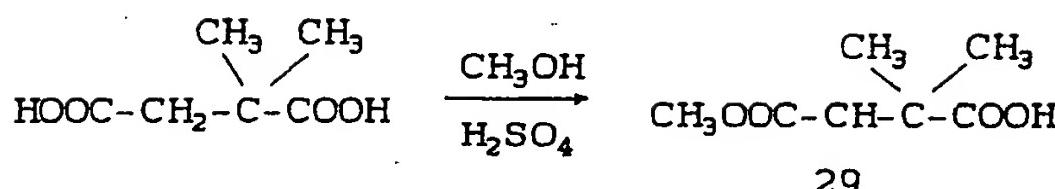


The protected amino acid derivatives IV are, in many cases, commercially available in t-butoxycarbonyl (BOC) or benzyloxycarbonyl (CBz) forms. A useful method to prepare the preferred sidechain 31 is shown in Scheme 10.

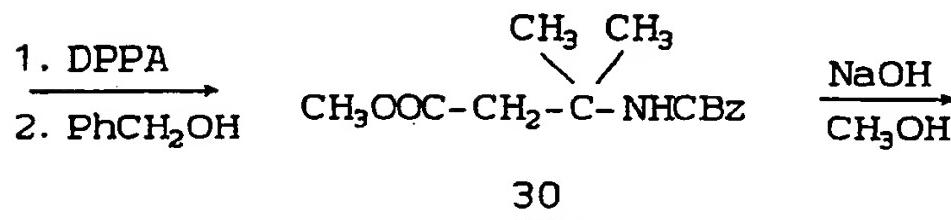
- 42 -

Scheme 10

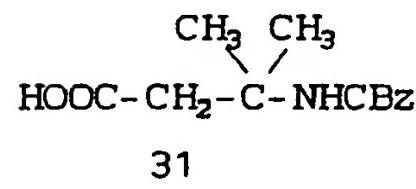
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Formation of the monomethyl ester 29 of 2,2-dimethylsuccinic acid is achieved by treatment of a methanolic solution with a catalytic amount of a strong acid, such as sulfuric acid. Treatment of 29 with diphenylphosphoryl azide (DPPA) followed by benzyl alcohol results in formation of the benzyloxycarbonyl (CBz) compound 30. Alkaline hydrolysis with sodium hydroxide in methanol affords the product 31.

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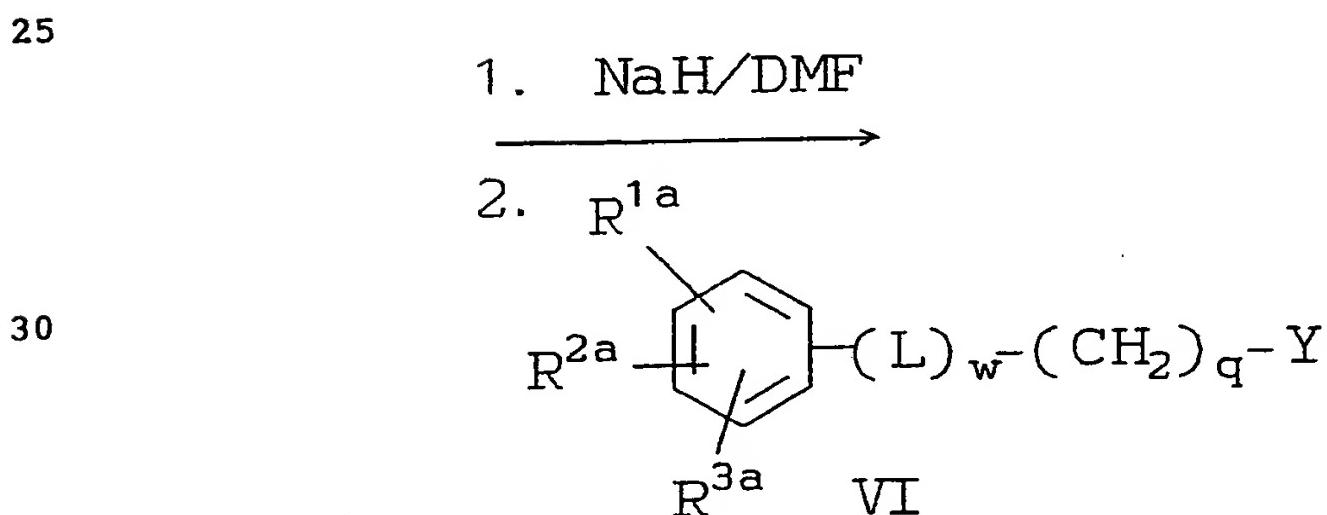
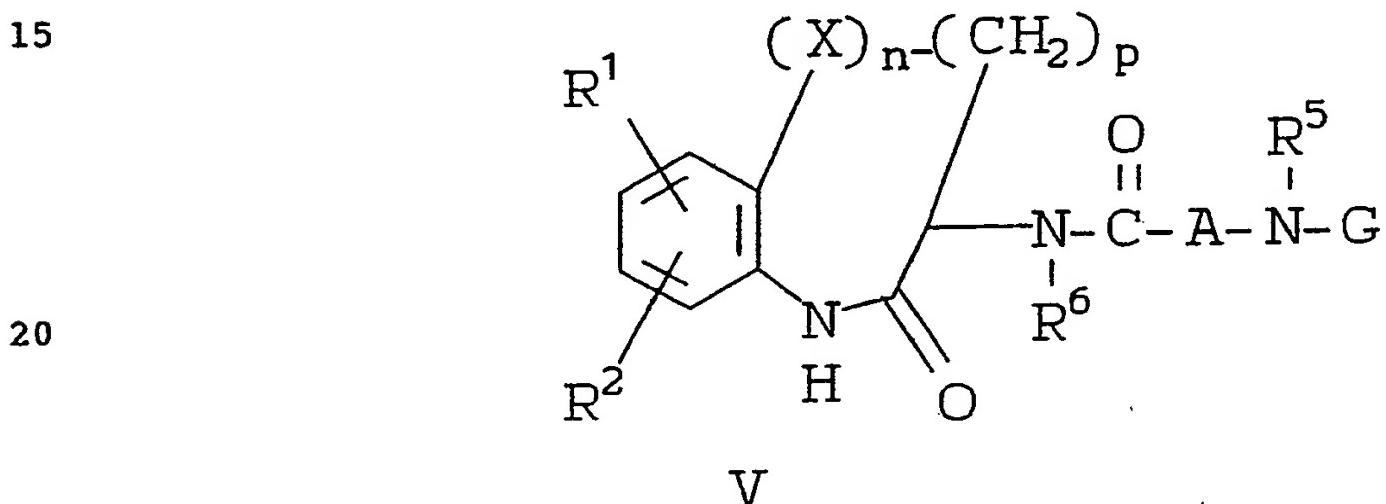
Intermediates of formula VII can be prepared as shown in Scheme 11 by treatment of the desired lactam intermediate V with an alkylating agent VI, wherein L is a good leaving group such as Cl, Br, I, O-methanesulfonyl or O-(p-toluenesulfonyl). Alkylation of intermediates of formula V is

- 43 -

conveniently carried out in anhydrous dimethyl formamide (DMF) in the presence of bases such as sodium hydride or potassium t-butoxide for a period of 0.5 to 24 hours at temperatures of 20-100°C.

5 Substituents on the alkylating agent VI may need to be protected during alkylation. A description of such protecting groups may be found in: Protective Groups in Organic Synthesis, T.W. Greene, John Wiley
10 and Sons, New York, 1981.

Scheme 11

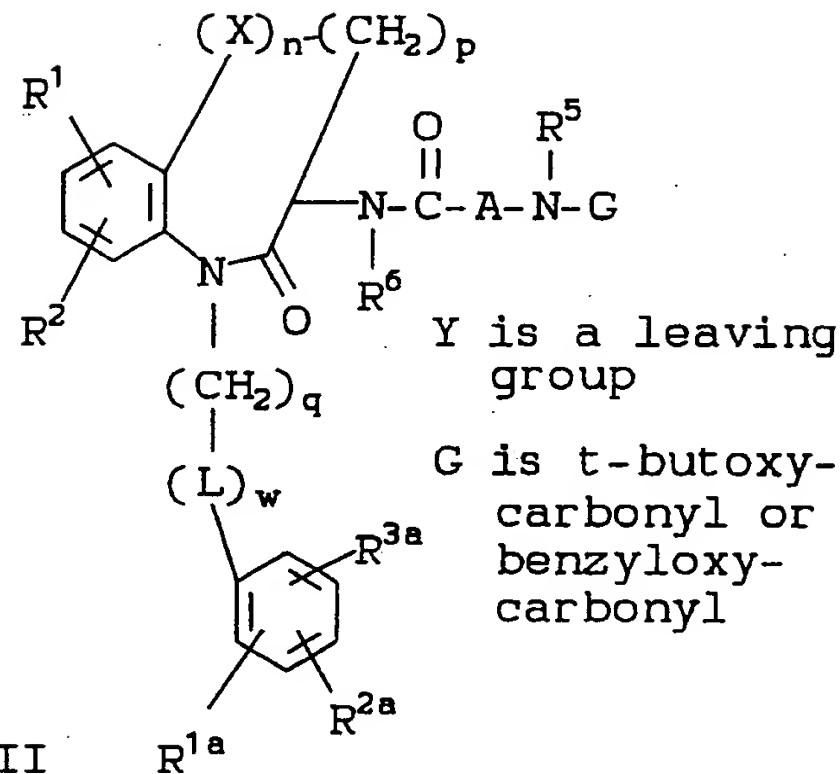


- 43/1 -

Scheme 11 (Cont'd)

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Alkylation agents VI are, in some cases
commercially available compounds or may be prepared
as described in EPO publications 253,310; 291,969;
5 324,377 and the references cited therein. A useful
method to prepare the preferred alkylating agent 36
is shown in reaction Scheme 12, and in U.S. Patent
5,039,814.

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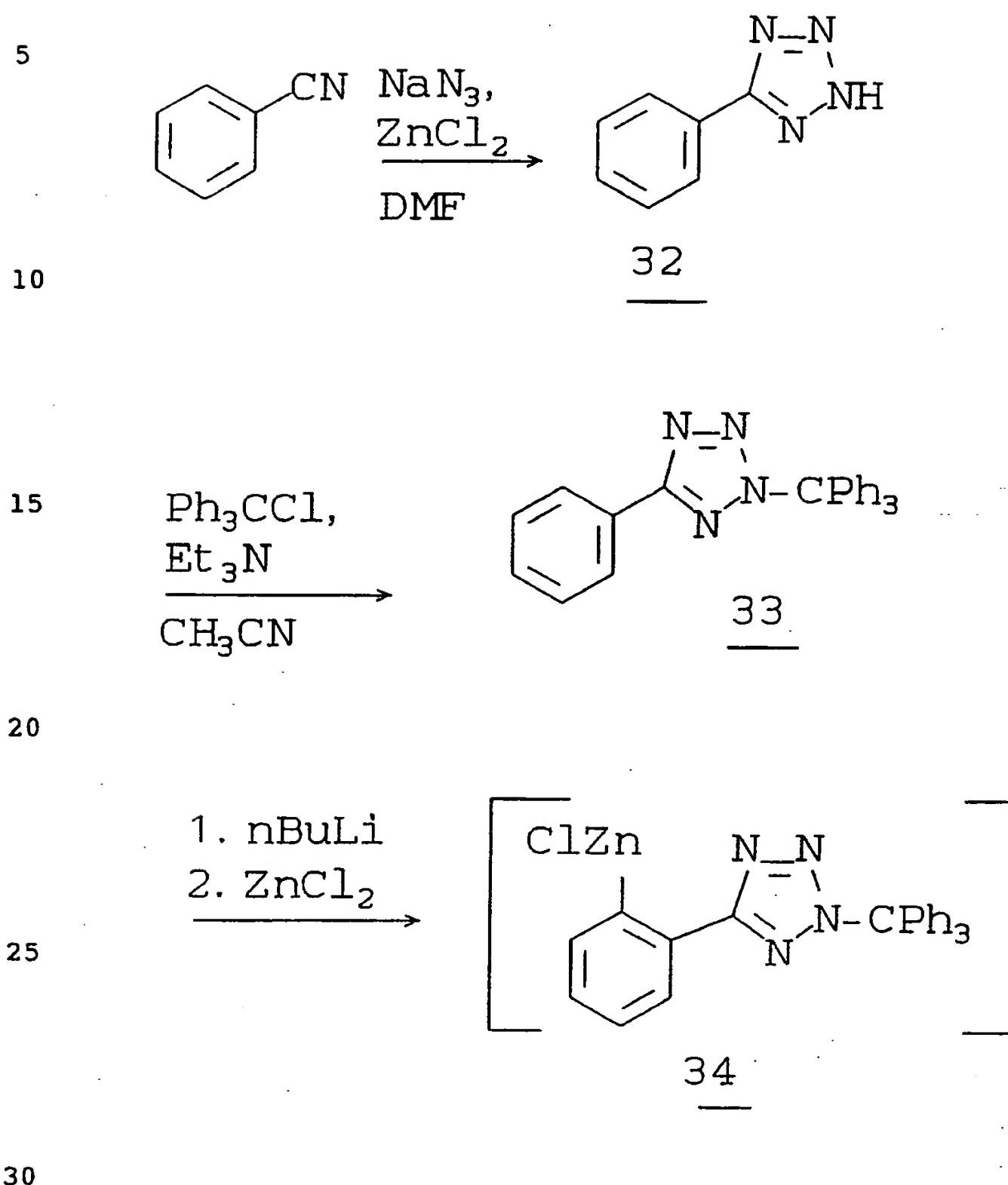
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Scheme 12

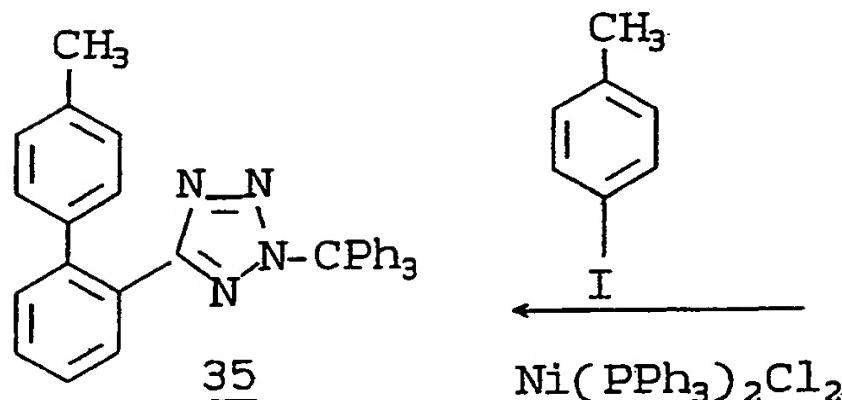


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Scheme 12 (Cont'd)

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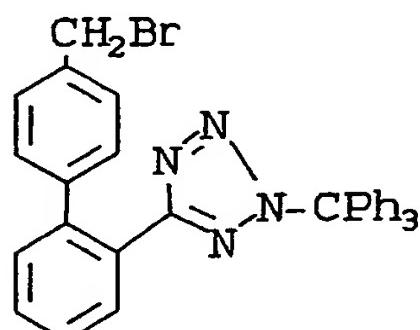
N-bromosuccinimide

AIBN

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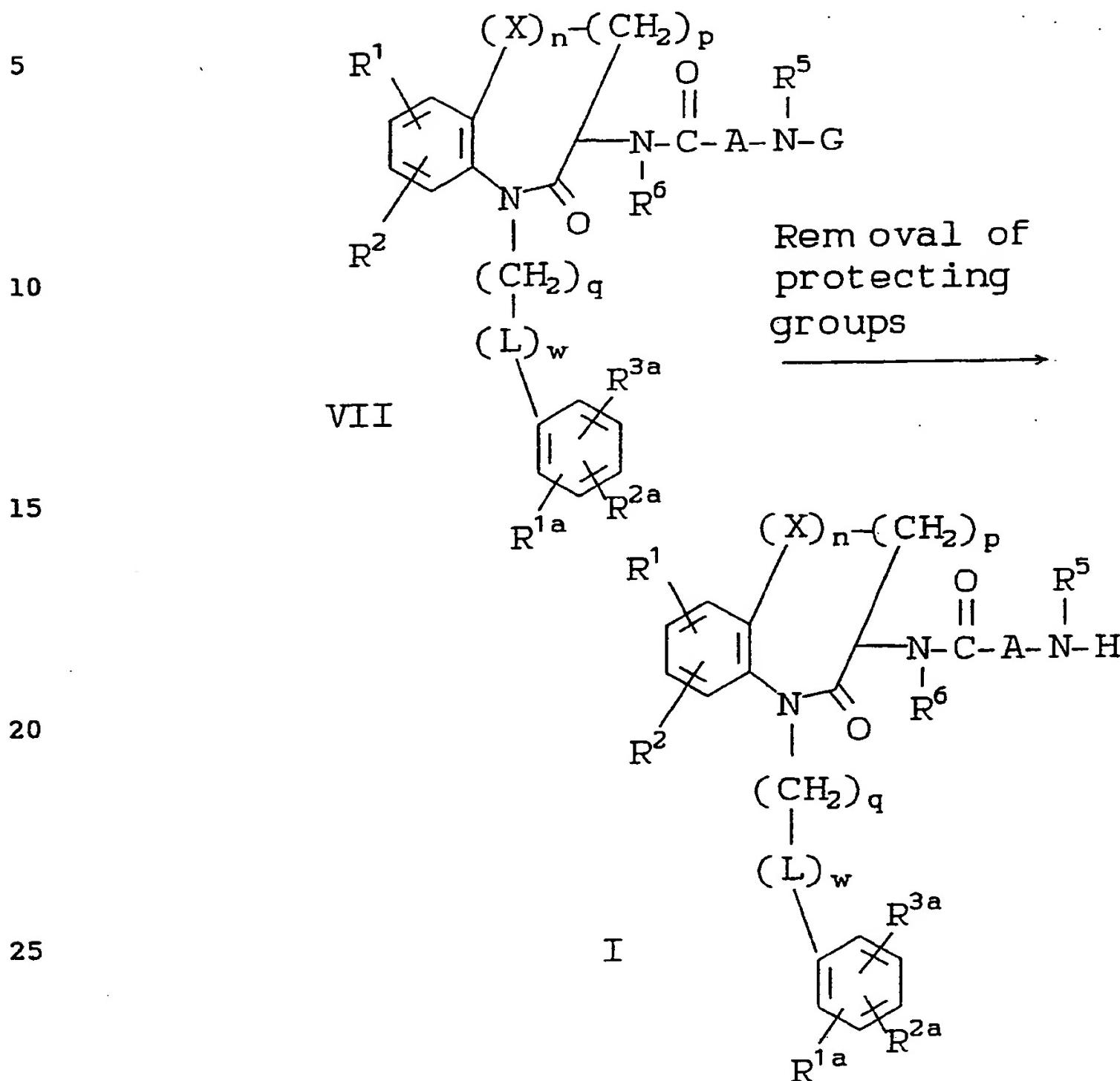
As outlined in Scheme 12, benzonitrile is treated with sodium azide and zinc chloride to give 5-phenyltetrazole 32 which is converted to the 5 N-trityl derivative 33 by treatment with triphenylmethyl chloride and triethylamine. The zinc reagent 34 was prepared by treatment with n-butyl lithium followed by zinc chloride. Coupling with 10 4-iodotoluene using the catalyst bis(triphenylphosphine)-nickel(II) dichloride gives the biphenyl product 35 in high yield. Reaction with N-bromosuccinimide and AIBN gives bromide 36.

Conversion to the final products of formula I wherein R⁴ is hydrogen, is carried out by 15 simultaneous or sequential removal of all protecting groups from intermediate VII as illustrated in Scheme 13. Removal of benzyloxycarbonyl groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in 20 the presence of a platinum or palladium catalyst in a protic solvent such as methanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of benzyloxycarbonyl groups can also be 25 achieved by treatment with a solution of hydrogen bromide in acetic acid. Catalytic hydrogenation is also employed in the removal of N-triphenylmethyl (trityl) protecting groups. Removal of t-butoxycarbonyl (BOC) protecting groups is carried 30 out by treatment of a solution in a solvent such as methylene chloride or methanol, with a strong acid, such as hydrochloric acid or trifluoroacetic acid. Conditions required to remove other protecting groups which may be present can be found in Protective Groups in Organic Synthesis.

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Scheme 13



30 Compounds of formula I wherein R⁴ and R⁵ are each hydrogen can be further elaborated by reductive alkylation with an aldehyde by the aforementioned procedures or by alkylations such as by reaction with various epoxides. The products, obtained as

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hydrochloride or trifluoroacetate salts, are
conveniently purified by reverse phase high
performance liquid chromatography (HPLC) or by
5 recrystallization.

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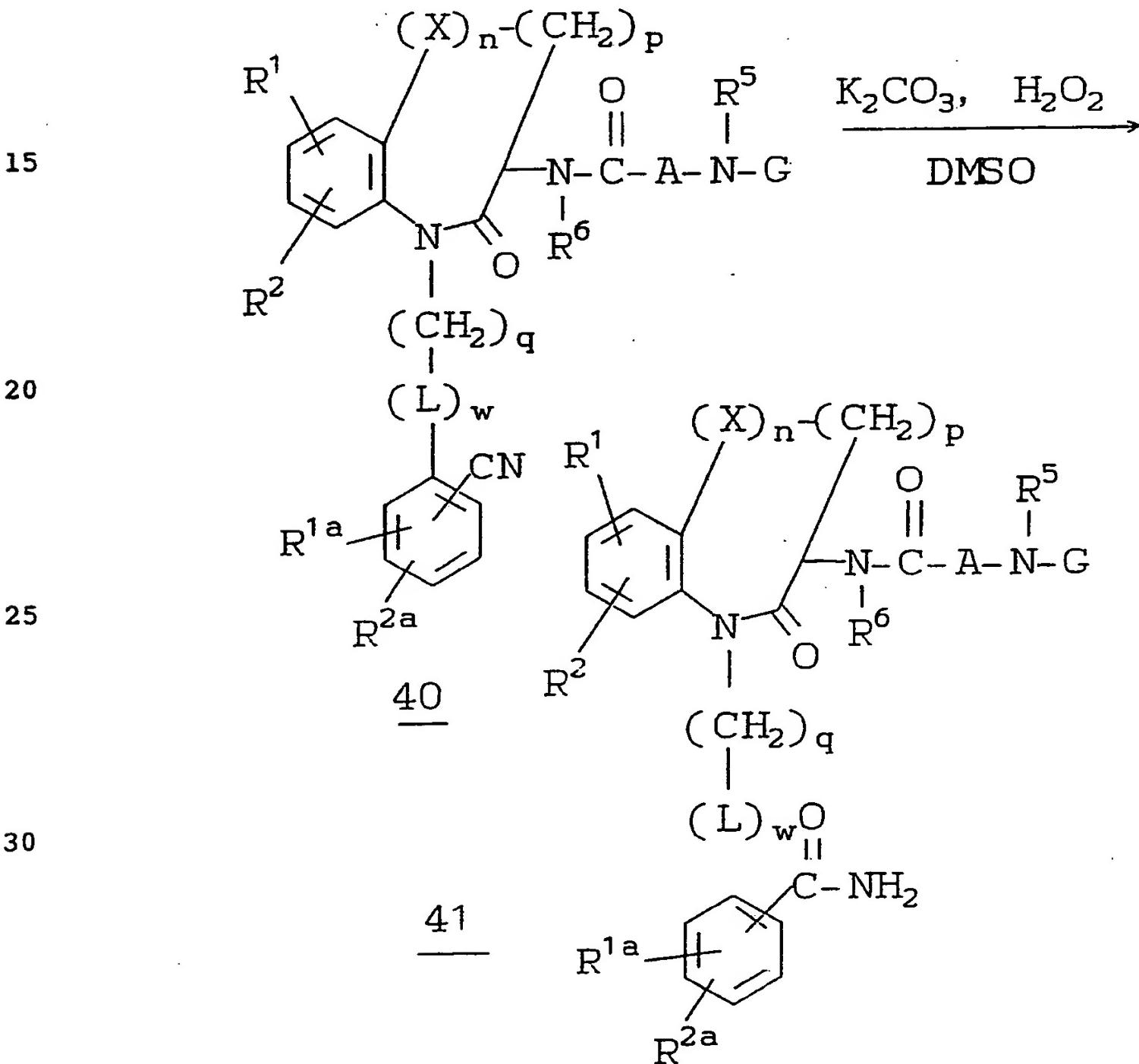
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Compounds of Formula I wherein R^{3a} or R^{3b} are taken as R⁴R⁵NCO(CH₂)_v and v is 0 can be prepared by several methods. For example, as shown in Scheme 14, compound 41 wherein R⁴ and R⁵ are both hydrogen is conveniently prepared by hydrolysis of a nitrile precursor 40.

Scheme 14

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Thus, treatment of the nitrile 40 with
hydrogen peroxide and a strong base, such as
potassium carbonate, in a polar solvent, such as
5 dimethylsulfoxide at temperatures of 25°C to 150°C

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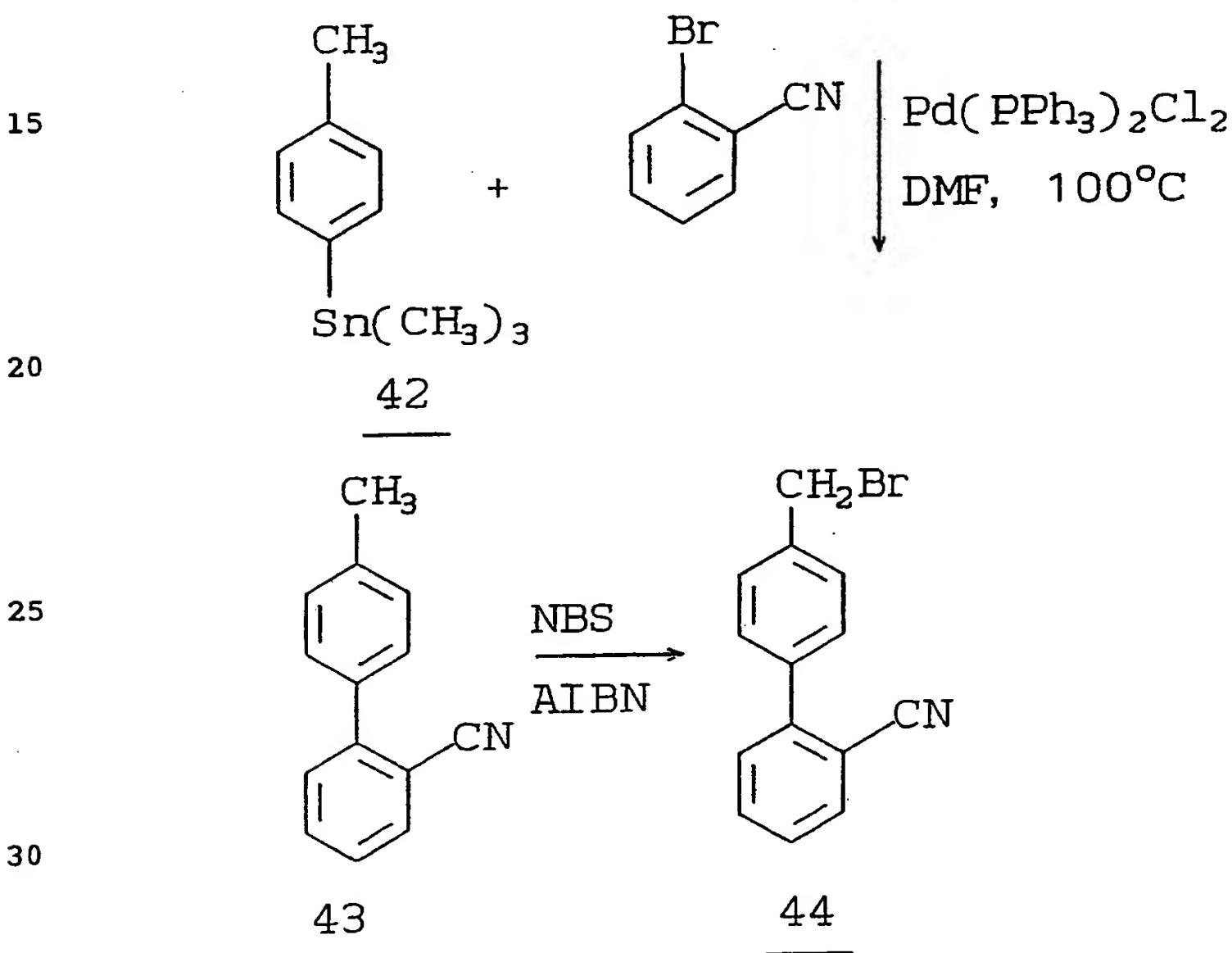
- 49 -

results in formation of the amide derivative 41. The precursor 40 can be prepared from an appropriate alkylating agent VI, where R^{3a} is cyano, as described in Scheme 11.

A useful method of preparing the alkylating agent 44 is outlined in Scheme 15.

Scheme 15

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Thus, treatment of 4-(methylphenyl)trimethyl
stannane 42 with 2-bromobenzonitrile in
dimethylformamide at 100°C in the presence of
5 bis-triphenylphosphine palladium (II) chloride
results in coupling to form the biphenyl nitrile 43
in high yield. Conversion to bromide 44 is achieved
by treatment with N-bromosuccinimide and a radical

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- 50 -

initiator, such as azobisisobutyronitrile (AIBN), in refluxing carbon tetrachloride.

Compounds of Formula I wherein R^{3a} or R^{3b} are taken as R⁴R⁵NCO(CH₂)_v and v is 0 and R⁴ and/or R⁵ are not hydrogen are prepared from the corresponding carboxylic acid derivatives 45 as shown in Scheme 16.

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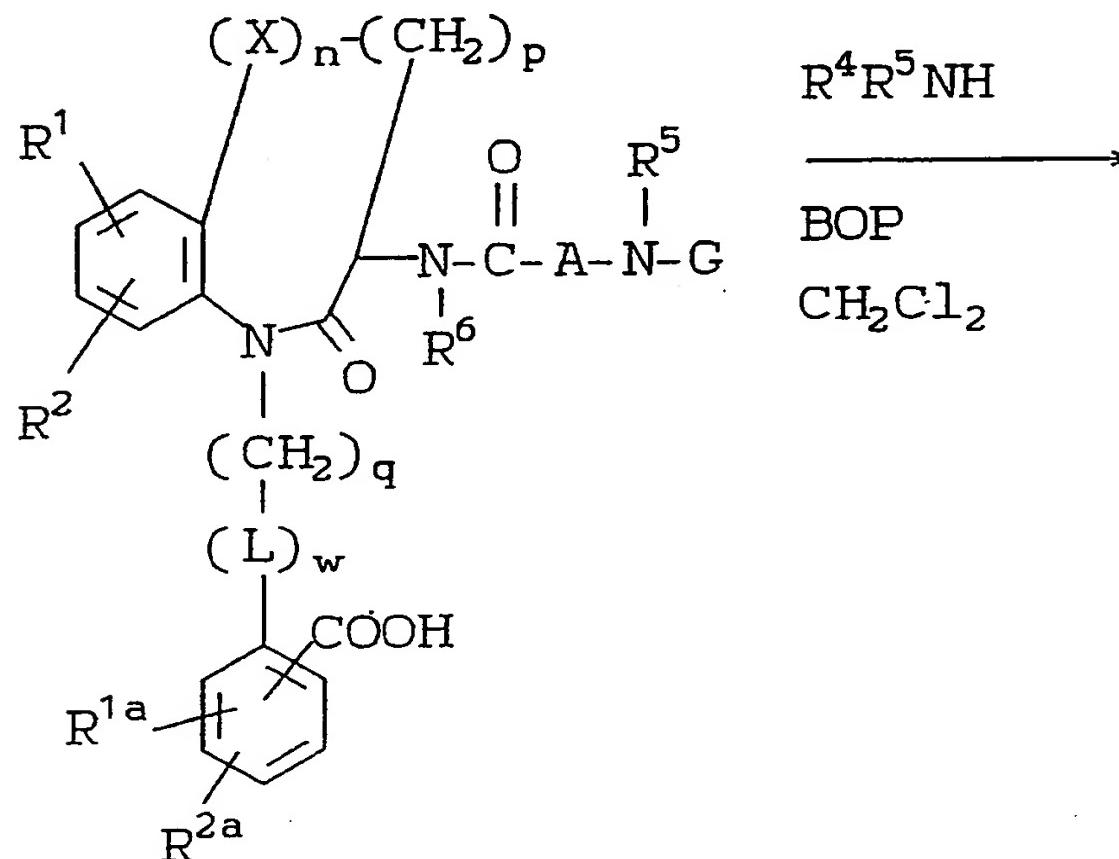
Scheme 16

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SCHEME 16 (Cont'd)

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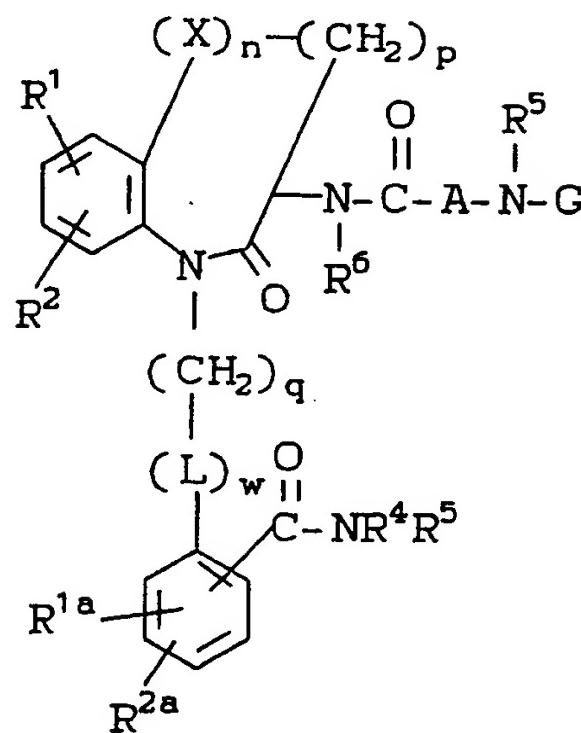
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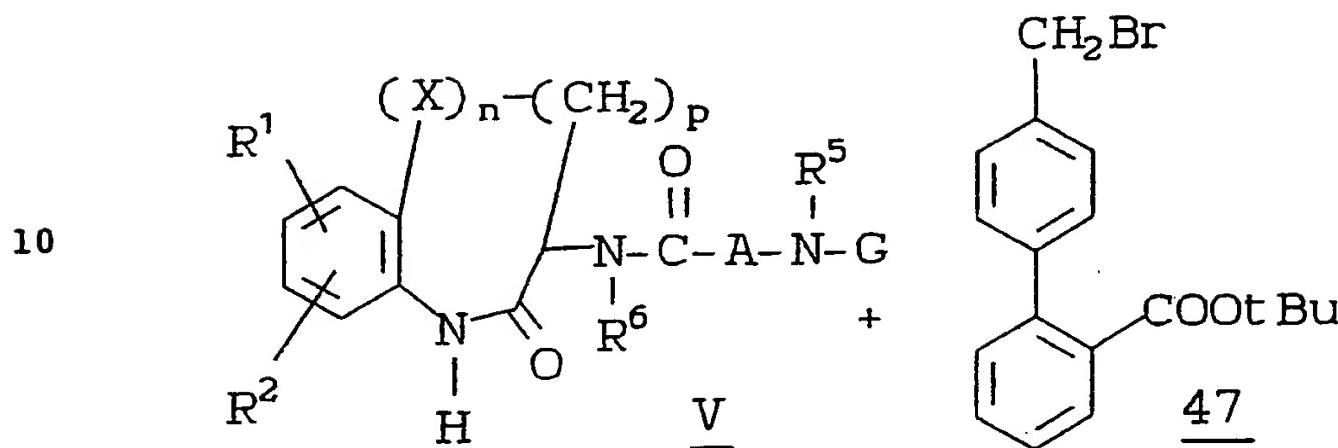
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Coupling of the carboxylic acid derivative 45 with R⁴R⁵NH is conveniently carried out by the use of a coupling reagent such as benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate ("BOP") in an inert solvent such as methylene chloride. The requisite carboxylic acid precursors can be prepared as illustrated in Scheme 17 for the biphenyl compound 49.

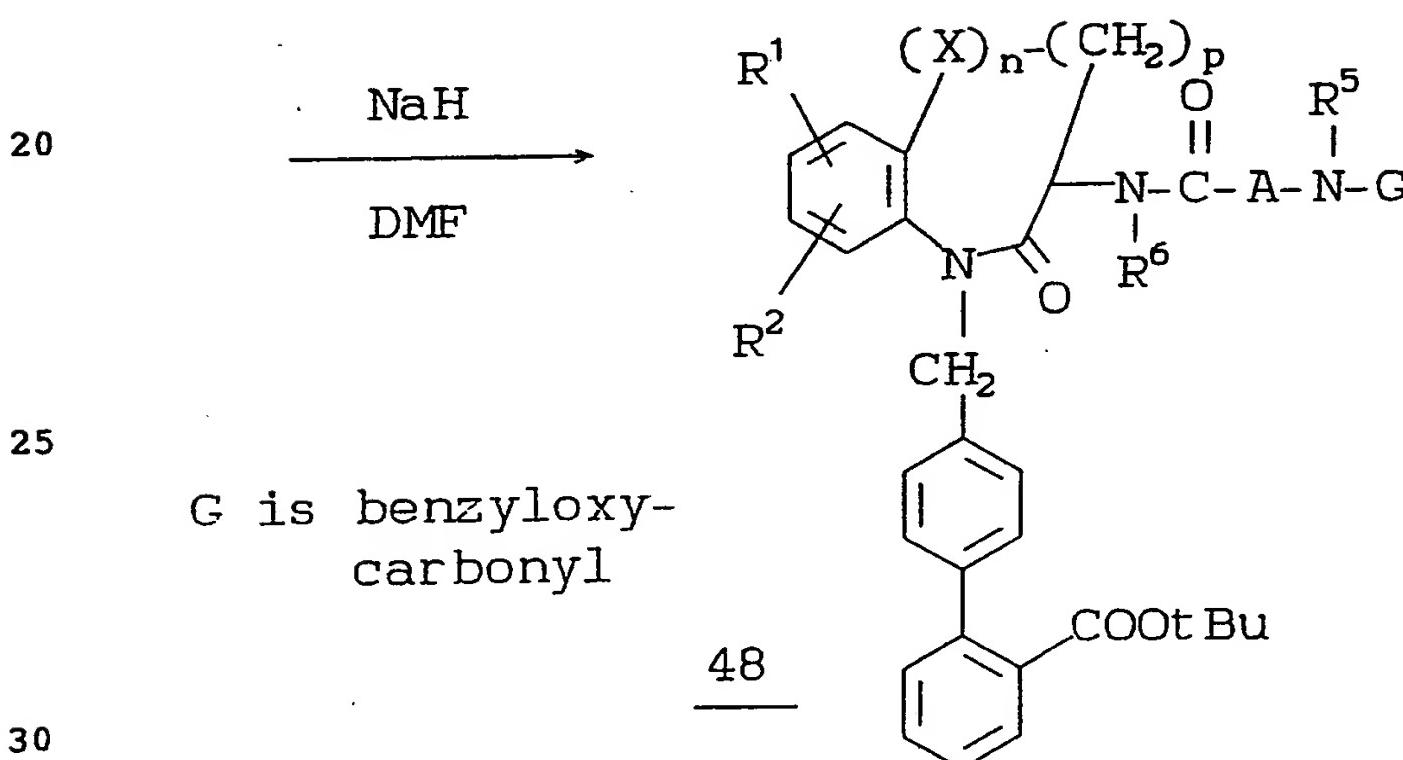
- 51 -

Scheme 17

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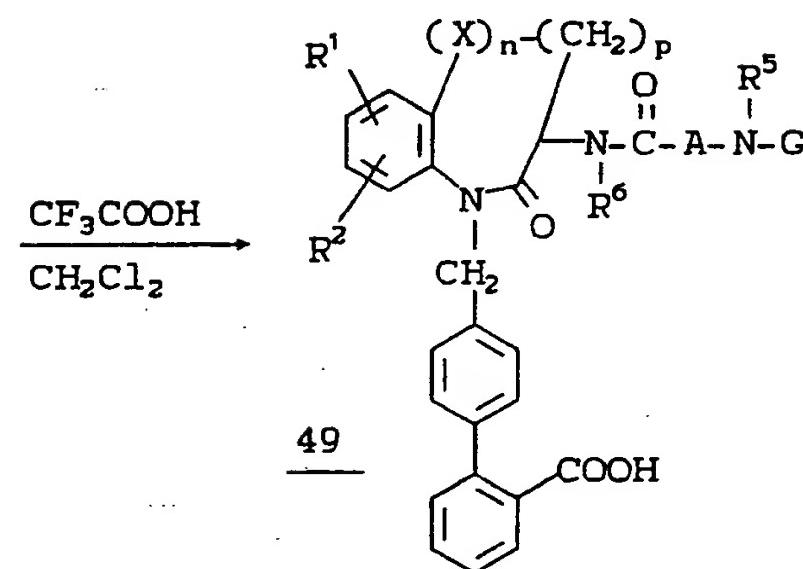
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Scheme 17 (Cont'd)

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Alkylation of V with t-butyl 4'-bromomethyl-biphenyl-2-carboxylate 47 (prepared as described in EPO Publication 324,377) in the presence of sodium hydride as previously described in Scheme 11 gives
5 the adduct 48 in high yield. Hydrolysis of the t-butyl ester is conveniently achieved by treatment with a strong acid, such as trifluoroacetic, in an inert solvent such as methylene chloride. It is
10 noted that the protecting group G in this instance must be inert to strongly acidic conditions, for example G is benzyloxycarbonyl (CBz). A useful preparation of the chiral intermediate 54 is shown in Scheme 18.

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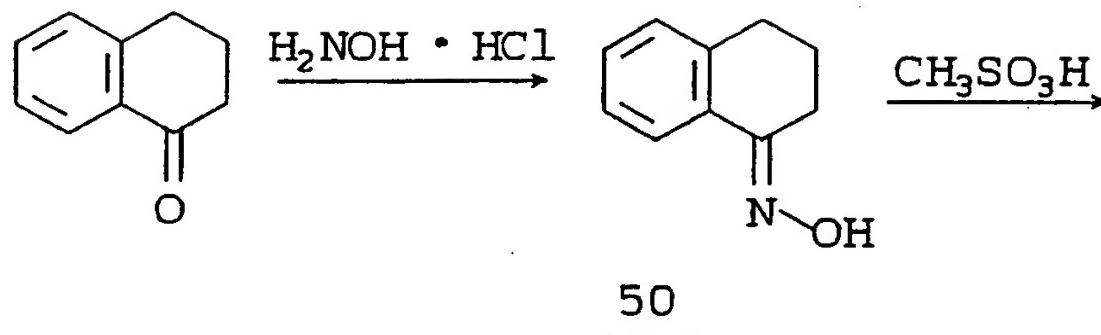
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Scheme 18

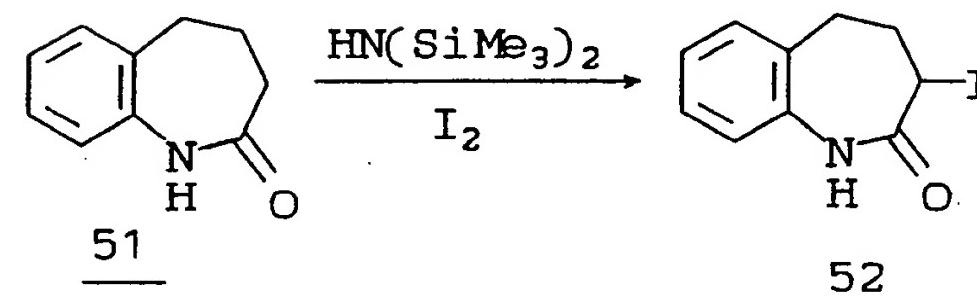
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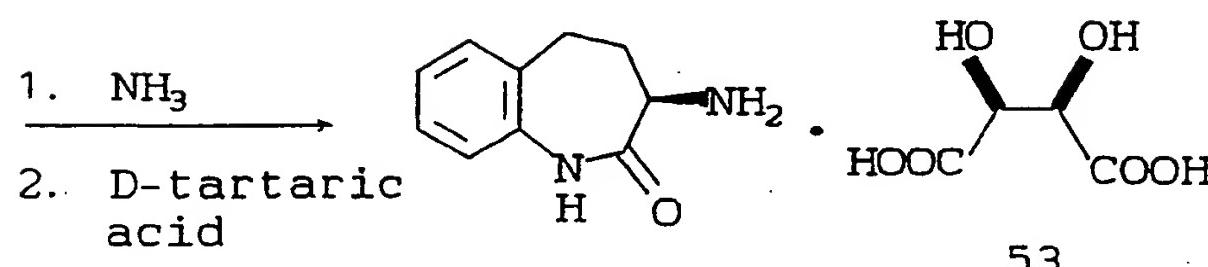
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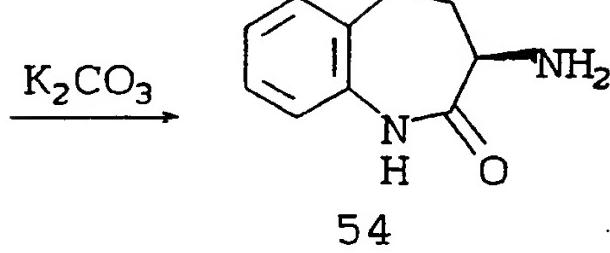
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Conversion of 1-tetralone to the seven-membered benzolactam 51 is achieved by Beckman rearrangement of the intermediate oxime 50.

5 Treatment of 51 with iodine and hexamethyldisilazane gives the 3-iodo derivative 52 which is sequentially treated with ammonia and D-tartaric acid to give the diastereomeric D-tartrate salt 53 after recrystallization. Liberation of the free amine 54 is achieved by neutralization of the D-tartrate salt 10 with potassium carbonate followed by extractive isolation.

15 An improved route to compounds containing the 3-amino-3-methylbutanamide sidechain is presented in Scheme 19.

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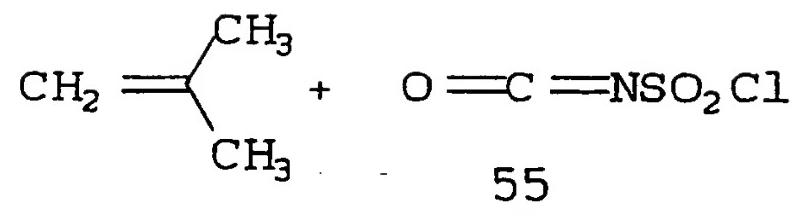
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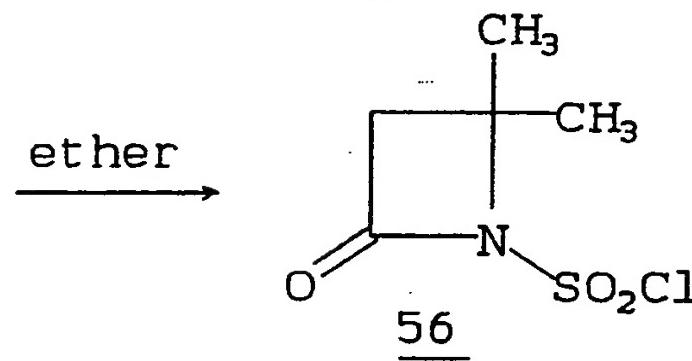
- 55 -

Scheme 19

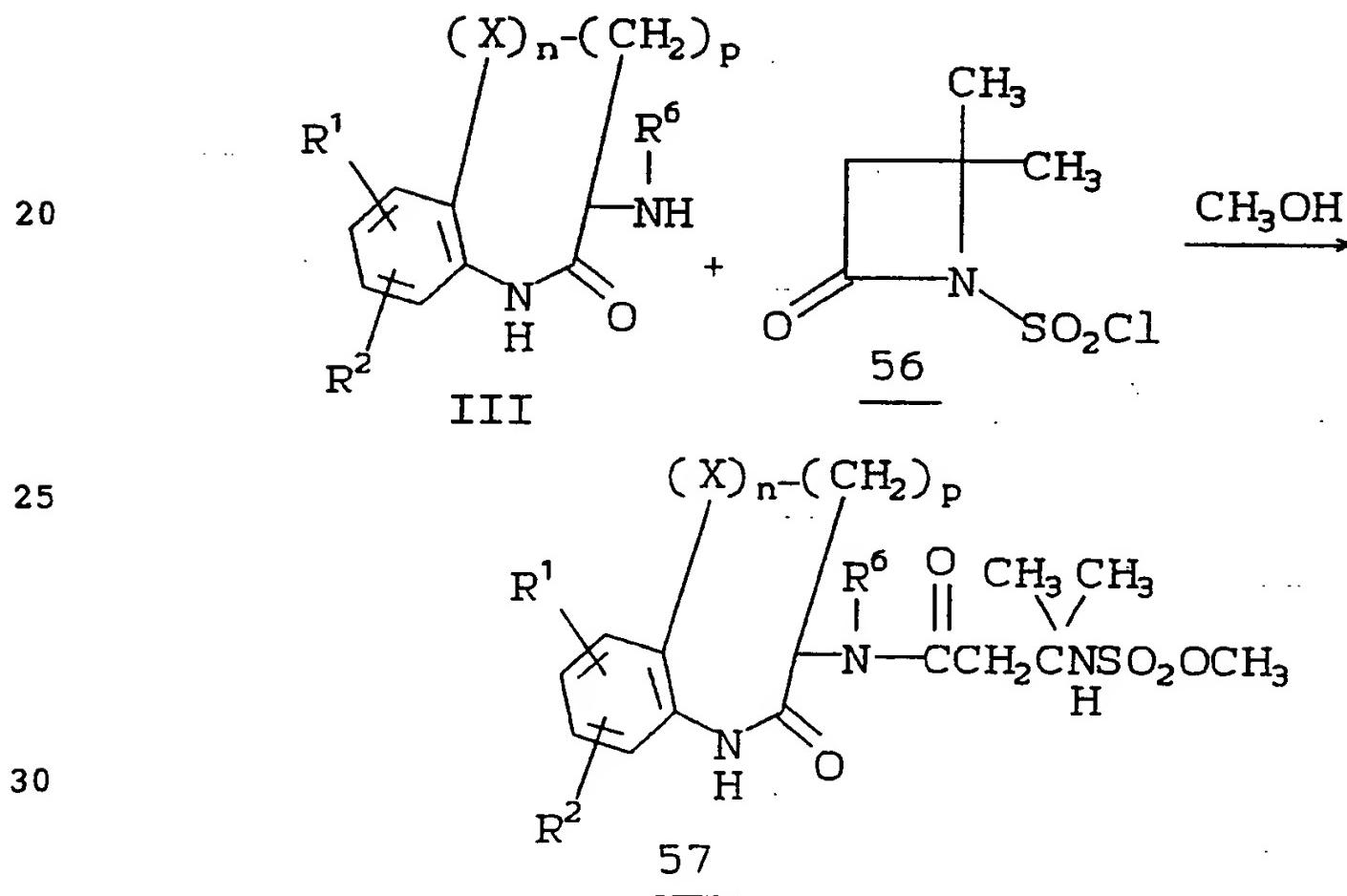
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- 56 -

Reaction of isobutylene with N-chlorosulfonylisocyanate 55 in ether gives the azetidinone derivative 56. Intermediates of Formula III can then be reacted with 56 to give the 3-methyl-3-amino-
5 butanamide intermediates 57 directly. Removal of the methoxysulfonyl auxilliary is conveniently achieved by treatment with aqueous acid, for example, 6N hydrochloric acid. The methoxysulfonyl group also
10 functions as a protection group G which is inert to the basic conditions employed in the subsequent alkylation step as illustrated in Scheme 11.

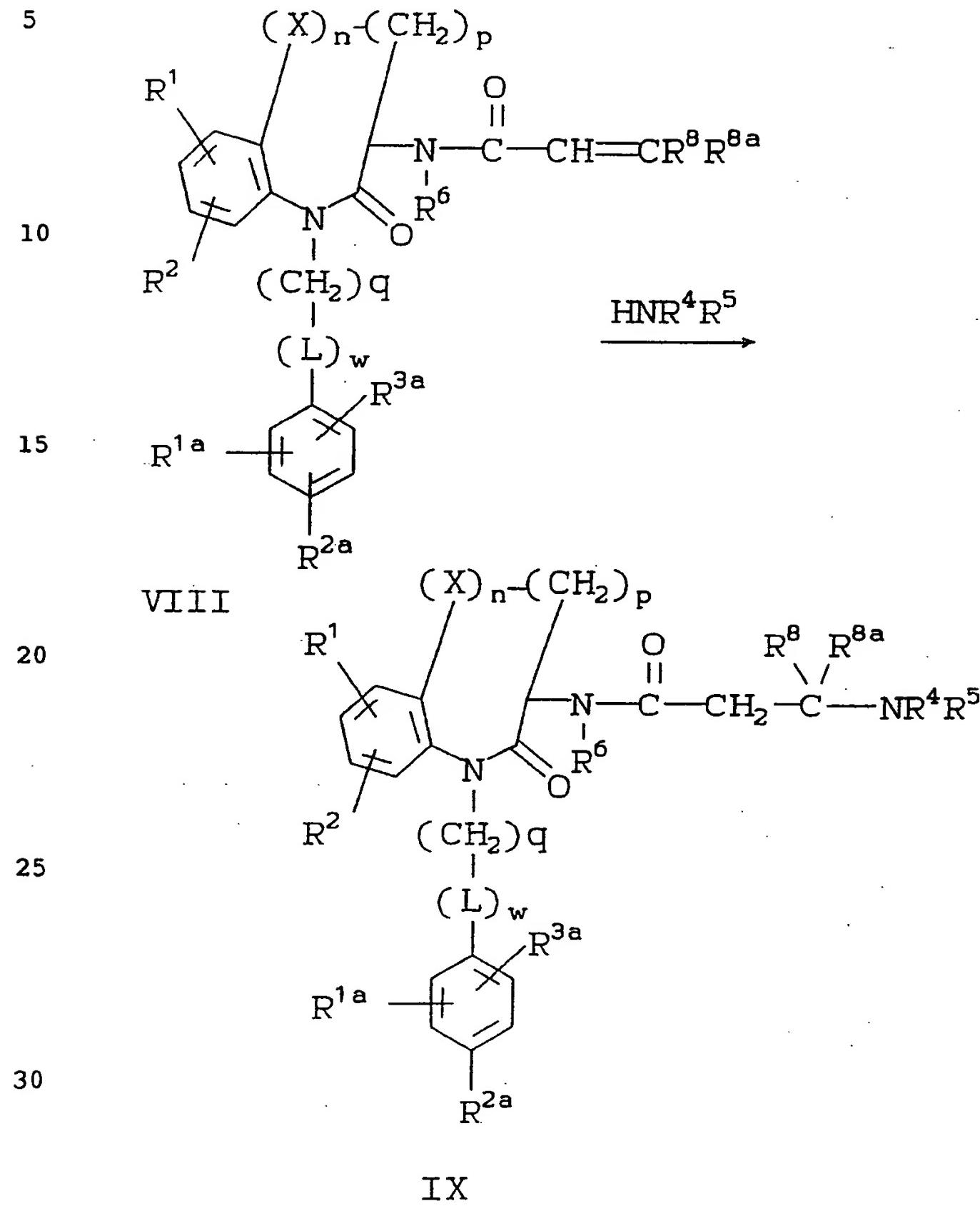
An alternate route to the sub-class of compounds of Formula I that can be described by
15 Formula IX is shown in Scheme 20.

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Scheme 20

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Thus, reaction of intermediates of Formula VIII with HNR⁴R⁵ neat or in a polar solvent such as dimethylsulfoxide at temperatures of 50°C to 200°C, results in a Michael addition to give compounds of Formula IX. Compounds of Formula VIII may themselves be prepared by the transformations illustrated in Schemes 9 and 11.

It is noted that the order of carrying out the foregoing reaction schemes is not significant and it is within the skill of one skilled in the art to vary the order of reactions to facilitate the reaction or to avoid unwanted reaction products.

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The growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive intestinal peptides, e.g., bombesin; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

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The compounds of Formula I can be administered to animals, including man, to release growth hormone in vivo. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, and to increase milk production in such animals. In addition, these compounds can be administered to humans in vivo as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered in vivo to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise a growth promoting agent in addition to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic or other pharmaceutically active material.

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Growth promoting agents include, but are not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeronol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the disclosed novel benzo-fused lactam growth hormone secretagogues is in combination with other growth hormone secretagogues such as GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890; and publications WO 89/07110 and WO 89/07111 and B-HT920 or growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: stimulating growth hormone release in elderly humans; Prevention of catabolic side effects of glucocorticoids, treatment of osteoporosis, stimulation of the immune system, treatment of retardation, acceleration of wound healing, accelerating bone fracture repair, treatment of growth retardation, treating renal failure or insufficiency resulting in growth retardation, treatment of physiological short

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stature, including growth hormone deficient children,
treating short stature associated with chronic
illness, treatment of obesity and growth retardation
associated with obesity, treating growth retardation
associated with Prader-Willi syndrome and Turner's
syndrome; Accelerating the recovery and reducing
hospitalization of burn patients; Treatment of
intrauterine growth retardation, skeletal dysplasia,
hypercortisolism and Cushings syndrome; Induction of
pulsatile growth hormone release; Replacement of
growth hormone in stressed patients; Treatment of
osteochondrodysplasias, Noonans syndrome,
schizophrenia, depression, Alzheimer's disease,
delayed wound healing, and psychosocial deprivation;
treatment of pulmonary dysfunction and ventilator
dependency; Attenuation of protein catabolic response
after a major operation; reducing cachexia and
protein loss due to chronic illness such as cancer or
AIDS. Treatment of hyperinsulinemia including
nesidioblastosis; Adjuvant treatment for ovulation
induction; To stimulate thymic development and
prevent the age-related decline of thymic function;
Treatment of immunosuppressed patients; Improvement
in muscle strength, mobility, maintenance of skin
thickness, metabolic homeostasis, renal hemeostasis
in the frail elderly; Stimulation of osteoblasts,
bone remodelling, and cartilage growth; Stimulation
of the immune system in companion animals and
treatment of disorders of aging in companion animals;
Growth promotant in livestock; and stimulation of
wool growth in sheep.

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The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, 5 sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration 10 include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also 15 comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets 20 and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration 25 include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for 30 parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions.

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Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 100 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone.

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The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

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Example 1

10 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yll-butanamide, trifluoroacetate

Step A: 3-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

15 A solution of 9.22 g (45.6 mmol) of 3-azido-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (prepared by the method of Watthey, et al., J. Med. Chem., 28, 1511-1516 (1985)) in 30mL methanol was hydrogenated at 40psi in the presence of 1.0g of 5% Pt/C for 4.5 hours. Celite was added and the mixture 20 filtered through a pad of Celite. The filtrate was concentrated and allowed to stand for 16 hours at room temperature which resulted in formation of crystals. The material was isolated by filtration and dried under vacuum to afford 4.18g (23.7mmol, 52%) of the product. The mother liquors were diluted to 100mL with methanol, treated with 2g of charcoal, filtered through Celite and the filtrate concentrated under vacuum to approximately 15 mL. A second crop formed yielding 2.02 g of product (11.5mmol, 25%). 25 Another recycling of the mother liquors afforded a third crop of 0.88g (5.0, 11%). A total of 7.08g (40.2mmol, 88%) of the product was thus obtained.
30 ^1H NMR (200MHz, CDCl_3): 1.6 (br s, 2H), 1.80 (m, 1H),

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2.55 (m, 2H), 2.88 (m, 1H), 3.42 (dd; 7Hz, 11Hz; 1H), 6.98 (d, 8Hz, 1H), 7.2 (m, 3H), 8.3 (br s, 1H). FAB-MS:
calculated for C₁₀H₁₂N₂O 176; found 177 (M+H, 100%).

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Step B: 3(R)-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

2.37g (13.5mmol) of 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Step A) and 2.02g (13.5mmol) of L-tartaric acid were suspended in 40mL of ethanol. The mixture was gently heated and complete dissolution achieved by dropwise addition of 5mL of distilled water. The solution was cooled to room temperature and aged overnight. The solid that formed was removed by filtration, washed with ethanol/diethyl ether (1:1) and dried under vacuum to afford 1.75g of crude L-tartrate salt. The mother liquors were evaporated to dryness under vacuum, redissolved in 40mL of water and the pH adjusted to 10-11 by the addition of solid potassium carbonate. The mixture was extracted with chloroform (6x20mL) and the combined extracts washed with water (1x) and brine (1x), dried over potassium carbonate, filtered and solvents removed under vacuum to afford 1.29g (7.33mmol) of partially enriched 3(R) amine.

25 The original 1.75g batch of L-tartrate salt was recrystallized twice from aqueous ethanol to afford 1.03g (3.17mmol, 24%) of purified L-tartrate salt with [a]_D=-212° (c=1, H₂O). The purified L-tartrate salt was dissolved in 20mL of water and the pH adjusted to 10-11 by the addition of solid potassium carbonate. The mixture was extracted with chloroform (5x10mL); combined extracts were washed

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with water and brine then dried over potassium carbonate, filtered and solvents removed under vacuum to afford 522mg (2.96mmol, 22% overall) of the 3(S) amine, $[a]_D^{-}446^{\circ}$ (c=1, CH₃OH).

The remaining 1.29g (7.33mmol) of partially enriched 3(R) amine was treated with 1.10g (7.33mmol) of D-tartaric acid as described above and the resulting salt recrystallized twice from aqueous ethanol to afford 1.20g of purified D-tartrate salt, $[a]_D^{-}214^{\circ}$ (c=1, H₂O). The purified D-tartrate salt was dissolved in 20mL of water and the free base isolated as described above to give 629mg (3.57mmol, 26% overall) of the 3(R) amine, $[a]_D^{+}455^{\circ}$ (c=1, CH₃OH).

Step C: 2,2-Dimethylbutanedioic acid, 4-methyl ester
2,2-dimethylsuccinic acid (20g, 137mmol) dissolved in 200mL absolute methanol at 0° was treated dropwise with 2mL concentrated sulfuric acid. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 16 hours.

The mixture was concentrated in vacuo to 50mL and slowly treated with 200mL of saturated aqueous sodium bicarbonate. The mixture was washed with hexane (3x) and the aqueous layer removed and cooled in an ice bath. The mixture was acidified to pH 2 by slow addition of 6N HCl then extracted with ether (8x). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and solvents removed in vacuo. The residue was dried at room temperature under vacuum to afford 14.7g

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(91.8mmol, 67%) of a viscous oil that slowly solidified upon standing. ^1H NMR analysis indicates the product is a mixture of the title compound and 15% of the isomeric 2,2-dimethylbutanedioic acid, 1-methyl ester. NMR (200MHz, CDCl_3) of title compound: 1.29 (s,6H), 2.60 (s,2H), 3.66 (s,3H). NMR (200MHz, CDCl_3) of isomer: 1.28 (s,6H), 2.63 (s,2H), 3.68 (s,3H).

10 Step D: 3-[Benzylloxycarbonylamino]-3-methylbutanoic acid, methyl ester

To 14.7g (91.8mmol) of 2,2-dimethylbutanedioic acid-4-methyl ester (Step C), containing 15% of the isomeric 1-methyl ester compound, in 150mL benzene was added 13mL of triethylamine (9.4g, 93mmol, 1.01eq) followed by 21.8mL diphenylphosphoryl azide (27.8g, 101mmol, 1.1eq). The mixture was heated under nitrogen at reflux for 45 minutes then 19mL (19.9g, 184mmol, 2eq) of benzyl alcohol was added and refluxing continued for 16 hours.

The mixture was cooled, filtered and the filtrate concentrated to a minimum volume under vacuum. The residue was redissolved in 250mL ethyl acetate, washed with water (1x), saturated aqueous sodium bicarbonate (2x) and brine (1x). The organic layer was removed, dried over magnesium sulfate, filtered and the filtrate concentrated to a minimum volume in vacuo. The crude product was purified by medium pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (4:1), to afford 18.27g (68.9mmol, 75%) of the title compound as a pale yellow liquid in addition to a small amount of

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pure 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester. ^1H NMR (200MHz, CDCl_3) of title compound: 1.40 (s,6H), 2.69 (s,2H), 3.63 (s,3H), 5.05 (s,2H), 5.22 (br s,1H), 7.32 (s,5H). ^1H NMR (200MHz, CDCl_3) of 3-[benzyloxycarbonylamino]-2,2-dimethylpropanoic acid, methyl ester (200MHz, CDCl_3): 1.19 (s,6H), 3.30 (d,7Hz,2H; resonance collapses to singlet in CD_3OD), 3.67 (s,3H), 5.09 (s,2H), 5.22 (br s,1H; resonance not observed in CD_3OD), 7.3 (br s,5H).

Step E: 3-Benzylloxycarbonylamino-3-methylbutanoic acid

A solution of 18.27g (68.9mmol) of methyl 3-benzylloxycarbonylamino-3-methylbutanoate (Step D) in 20mL of methanol at room temperature was treated dropwise with 51mL of 2N NaOH (102mmol, 1.5eq). The mixture was stirred at room temperature for 16 hours then transferred to a separatory funnel and washed with hexane (3x). The aqueous layer was removed, cooled to 0° and slowly acidified to pH 2 (paper) by dropwise addition of 6N HCl. This mixture was extracted with ether (6x); combined extracts were washed with 1N HCl and brine, then dried over magnesium sulfate, filtered and solvent removed under vacuum to afford 17.26g (68.7mmol, 99%) of the product. ^1H NMR (200MHz, CDCl_3): 1.42 (s,6H), 2.77 (s,2H), 5.06 (s,2H), 5.2 (br s,1H), 7.3 (s,5H).

Step F: 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

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To a solution of 252mg (1.43mmol) of
3(R)-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one
(Step B) in 4mL of methylene chloride at room
temperature was added 400mg (1.60mmol, 1.1eq) of
5 3-benzyloxycarbonylamino-3-methylbutanoic acid (Step
E) followed by 760mg (1.7mmol, 1.2eq) benzotriazol-1-
yloxytris(dimethylamino)phosphonium hexafluoro-
phosphate and 0.50mL of diisopropylethylamine (380mg,
10 2.9mmol, 2eq). After 3 hours at room temperature,
the mixture was diluted into 30mL of ethyl acetate
and washed with 5% aqueous citric acid, saturated
aqueous sodium bicarbonate (2x) and brine. The
organic layer was removed, dried over magnesium
15 sulfate, filtered and solvents removed under vacuum.
The residue was purified by medium pressure liquid
chromatography on silica, eluting with ethyl acetate
to afford 586mg (1.43mmol, 100%) of the product. ¹H
NMR (200MHz, CDCl₃): 1.38 (s, 3H), 1.39 (s, 3H), 1.82
20 (m, 1H), 2.52 (s, 2H), 2.5-3.0 (m, 3H), 4.51 (m, 1H),
5.07 (br s, 2H), 5.57 (br s, 1H), 6.68 (d, 7Hz, 1H), 6.97
(d, 8Hz, 1H), 7.1-7.4 (m, 8H), 7.61 (br s, 1H). FAB-MS:
calculated for C₂₃H₂₇N₃O₄ 409; found 410
(M+H, 100%); [a]_D=^{+137°} (c=1, CHCl₃).

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Step G: 5-Phenyltetrazole

Zinc chloride (3.3g, 24.3mmol, 0.5eq) was
added to 15mL of N,N-dimethylformamide in small
30 portions while maintaining the temperature below
60°C. The suspension of zinc chloride was cooled to
room temperature and treated with 5.0g of
benzonitrile (48.5mmol, 1.0eq) followed by 3.2g of
sodium azide (48.5mmol, 1.0eq). The heterogeneous
mixture was heated at 115°C with agitation for 18

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hours. The mixture was cooled to room temperature, water (30mL) was added and the mixture acidified by the addition of 5.1mL of concentrated hydrochloric acid. The mixture was cooled to 0°C and aged for one hour, then filtered and the filter cake washed with 15mL of cold 0.1N HCl then dried at 60°C under vacuum to afford 6.38g (43.7mmol, 90%) of the product.

10 Step H: 5-Phenyl-2-trityltetrazole

To a suspension of 5.0g (34.2mmol) of 5-phenyltetrazole in 55mL of acetone was added 5.0mL of triethylamine (3.6g, 35.6mmol, 1.04eq). After 15 minutes, a solution of 10.0g of triphenylmethyl chloride (35.9mmol, 1.05eq) in 20mL of tetrahydrofuran was added and the mixture stirred at room temperature for one hour. Water (75mL) was slowly added and the mixture stirred for one hour at room temperature. The product was collected by filtration, washed with 75mL of water and dried at 60°C under vacuum to give 13.3g (34.2mmol, 100%) of the product.

25 Step I: N-Triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)] tetrazole

A solution of zinc chloride (6.3g, 46.2mmol, 0.6eq) in 35mL of tetrahydrofuran was dried over molecular sieves. 5-Phenyl-2-trityltetrazole (30.0g, 77.3mmol, 1.0eq) was dissolved in 300mL of dry tetrahydrofuran and the solution gently stirred while being degassed three times by alternating vacuum and nitrogen purges. The stirred solution was cooled to

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5 -15°C and treated slowly with 50.5mL of 1.6M
n-butyllithium in hexane (80.0mmol, 1.05eq) so as to
maintain the temperature below -5°C. The solution
was maintained at -5 to -15°C for 1.5 hours then
treated with the dried zinc chloride solution and
allowed to warm to room temperature.

10 In a separate flask, 4-iodotoluene (20.17g,
92.5mmol, 1.2eq) and bis-(triphenylphosphine)nickel-
(II) dichloride (1.5g, 2.3mmol, 0.03eq) were
dissolved in 60mL of tetrahydrofuran, then degassed
and left under an atmosphere of nitrogen. The
mixture was cooled to 5°C and treated with 1.5mL of
3.0M solution of methylmagnesium chloride in
15 tetrahydrofuran (4.5mmol, 0.06eq) so as to keep the
temperature below 10°C. The solution was warmed to
room temperature and added, under nitrogen purge, to
the arylzinc solution. The reaction mixture was
stirred vigorously for 8 hours at room temperature
20 then quenched by the slow addition of a solution of
10mL of glacial acetic acid (1.6mmol, 0.02eq) in 60mL
of tetrahydrofuran at a rate so that the temperature
was maintained below 40°C. The mixture was stirred
for 30 minutes and 150mL of 80% saturated aqueous
25 sodium chloride was added; the reaction mixture was
extracted for 30 minutes and the layers allowed to
separate. The organic layer was removed and washed
with 150mL of 80% saturated aqueous sodium chloride
buffered to pH>10 by the addition of ammonium
30 hydroxide. The organic phase was removed and
concentrated under vacuum to approximately 50mL then
250mL of acetonitrile was added. The mixture was

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again concentrated under vacuum to 50mL and acetonitrile added to make the final volume 150mL. The resulting slurry was cooled at 5°C for 1 hour
5 then filtered and washed with 50mL of cold acetonitrile followed by 150mL of distilled water. The filter cake was air dried to a free flowing solid then further dried under vacuum at 50°C for 12 hours to afford 30.0g (62.8mmol, 81%) of the product. ¹H
10 NMR (200MHz, CDCl₃): 2.28 (s,3H), 6.9-7.05 (m,10H), 7.2-7.5 (m,12H), 7.9 (m,1H).

Step J: N-Triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl) tetrazole

15 A solution of 3.15g (6.6mmol) of N-triphenylmethyl-5-[2-(4'-methylbiphen-4-yl)]
tetrazole (Step I) in 25mL of methylene chloride was treated with 1.29g (7.25mmol, 1.1eq) of N-bromosuccinimide, 80mg (0.5mmol, 0.07eq) of AIBN,
20 200mg of sodium acetate and 200mg of acetic acid. The mixture was heated at reflux for 2 to 16 hours then cooled and washed with saturated aqueous sodium bicarbonate. The organic layer was removed, dried over sodium sulfate, filtered and concentrated to a minimum volume by atmospheric distillation. Methyl t-butyl ether was added and distillation continued until almost all the methylene chloride was removed the the total volume reduce to approximately 12mL and 12mL of hexanes was then added. The mixture was kept
25 at room temperature for 2 hours and the product isolated by filtration, washed with hexanes then dried under vacuum at 50°C to give 2.81g (5.04mmol,

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76%) of the product. ^1H NMR (200MHz, CDCl_3): 4.38 (s,2H), 6.9-8.0 (m,23H). NMR indicates presence of approximately 1% of the starting material and 7% of the dibromo derivative.

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Step K: 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide

To a solution of 437mg (1.07mmol) of the intermediate obtained in Step F in 2mL of dry dimethylformamide at room temperature under nitrogen was added 55mg of 60% sodium hydride oil dispersion (33mg NaH, 1.38mmol, 1.3eq). After 15 minutes, a solution of 715mg (1.28mmol, 1.2eq) N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole (Step J) in 1.5mL of dry dimethylformamide was added and the mixture stirred for 90 minutes.

The reaction mixture was added to 100mL of ethyl acetate and washed with water (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. Purification by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (1:1), afforded 902mg (1.02mmol, 95%) of the product. ^1H NMR (200MHz, CDCl_3): 1.38 (s,3H), 1.39 (s,3H), 1.68 (m,1H), 2.2-2.5 (m,5H), 4.44 (m,1H), 4.67 (d,14Hz,1H), 5.06 (s,2H), 5.12 (d,14Hz,1H), 5.63 (br 1,1H), 6.65 (d,8Hz,1H), 6.9-7.5 (m,31H), 7.85 (m,1H).

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Step L: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

5 A solution of 902mg (1.02mmol) of the intermediate obtained in Step H in 5mL methanol was hydrogenated at room temperature and one atmosphere over 160mg of 20% Pd(OH)₂/C for 14 hours. The mixture was filtered through Celite and concentrated under vacuum. The residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol over 10 minutes) to afford 568mg (0.91mmol, 89%) of the title compound.

10 ¹H NMR (200MHz, CD₃OD): 1.33 (s,3H), 1.37 (s,3H), 2.0-2.6 (m,6H), 4.35 (dd;7,11Hz;1H), 4.86 (d,15Hz,1H), 5.20 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.15-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calculated for C₂₉H₃₁N₇O₂ 509; found 510 (M+H,100%).

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Example 2

25 3-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-propanamide, mono(hydrochloride)

30 Step A 3-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-propanamide To a solution of 50mg (0.28mmol) 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1;

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Step A) in 2mL methylene chloride at room temperature was added 56mg (0.30mmol, 1.05eq) 3-(t-butoxycarbonyl-amino)propanoic acid followed by 0.1mL diisopropyl-ethylamine (74mg, 0.57mmol, 2eq) and 190mg (0.43mmol, 1.5eq) benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. After 1 hour at room temperature, the mixture was added to 20mL ethyl acetate and washed with 1M aqueous citric acid, saturated aqueous sodium bicarbonate and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed in vacuo. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (2:1) to afford 76mg (0.22mmol, 77%) of product as a white solid. ^1H NMR (200MHz, CDCl_3): 1.40 (s, 9H), 1.95 (m, 1H), 2.40 (t, 6Hz, 2H), 2.6-3.0 (m, 3H), 3.36 (q, 6Hz, 2H), 4.52 (m, 1H), 5.15 (br t, 1H), 6.58 (br d, 1H), 7.0-7.3 (m, 4H), 7.6 (br s, 1H). FAB-MS: calc. for $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_4$ 347; found 348 ($\text{M}+\text{H}$, 35%).

Step B 3-t-Butoxycarbonylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide
To a solution of 68mg (0.20mmol) of the intermediate obtained in Step A in 0.5mL dry dimethylformamide under nitrogen was added 10mg of 60% sodium hydride oil dispersion (6mg NaH, 0.25mmol, 1.3eq). After 15min., a solution of 142mg (0.26mmol, 1.3eq) N-triphenylmethyl-5-(4'-bromomethylbiphen-2-

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yl)tetrazole (Example 1, Step J) in 0.5mL
dimethylformamide was added and the mixture stirred
at room temperature for 4 hours. The mixture was
5 added to 30mL ethyl acetate and washed twice with pH
7.0 phosphate buffer and once with brine. The
organic layer was removed, dried over magnesium
sulfate filtered and solvents removed in vacuo. The
residue was purified by medium pressure liquid
10 chromatography on silica, eluting with ethyl acetate
to afford 152mg (0.18mmol, 94%) of the product as a
white foam. ^1H NMR (200MHz, CDCl_3): 1.40 (s, 9H),
1.77 (m, 1H), 2.3-2.6 (m, 5H), 3.35 (q, 6Hz, 2H), 4.45
15 (m, 1H), 4.70 (d, 15Hz, 1H), 5.12 (d, 15Hz, 1H), 6.53
(d, 7Hz, 1H), 6.9-7.5 (m, approx. 25H), 7.85 (m, 1H).

Step C 3-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-
20 propanamide

The intermediate obtained in Step B (150mg,
0.18mmol) dissolved in 5mL methanol was hydrogenated
over 30mg of $\text{Pd}(\text{OH})_2$ on carbon at one atmosphere for
2 hours. The mixture was filtered through Celite and
25 the filtrate concentrated under vacuum. The residue
was purified by medium pressure liquid chromatography
on silica, eluting with ethyl acetate/acetonitrile/
methanol (9:1:1) to afford 62mg (0.11mmol, 59%) of
the product as a colorless glass. ^1H NMR (200MHz,
30 CD_3OD): 1.39 (s, 9H), 2.0-2.5 (m, 6H), 3.26
(t, 7Hz, 2H), 4.31 (dd; 7, 12Hz; 1H), 4.83 (d, 16Hz, 1H),

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5.20 (d, 16Hz, 1H), 6.98 (d, 8Hz, 2H), 7.1-7.6 (m, 10H).

FAB-MS: calc. for $C_{32}H_{35}N_7O_4$ 581; found 582
(M+H, 19%).

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Step D 3-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3-yl]-propanamide,
mono(hydrochloride)

10

To a solution of 40mg (0.07mmol) of the intermediate obtained in Step C in 2mL methanol at room temperature was added 0.5mL of concentrated hydrochloric acid and the mixture stirred for 16 hours. All volatiles were removed under vacuum and the residue further dried under high vacuum to afford 35mg (0.07mmol, 100%) of the title compound as a pale yellow glass. 1H NMR (200MHz, CD₃OD): 2.0-2.8 (m, 6H), 3.22 (t, 6Hz, 2H), 4.30 (dd; 7, 10Hz; 1H), 4.83 (d, 16Hz, 1H), 5.17 (d, 16Hz, 1H), 6.97 (d, 8Hz, 2H), 7.1-7.6 (m, 10H). FAB-MS: calc. for $C_{27}H_{27}N_7O_2$ 481; found 482 (M+H, 100%).

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Example 3

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3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-(phenylmethyl)-1H-1-benzazepin-3(R)-yl]-butanamide,
trifluoroacetate

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Step A: 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-(phenylmethyl)-1H-1-benzazepin-3(R)-yl]-butanamide

To a solution of 40mg (0.098mmol) of

3-benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetra-

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hydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide
(Example 1, Step F) in 0.5mL of dry dimethylformamide
at room temperature under nitrogen was added 5mg of
5 60% sodium hydride oil dispersion (3mg NaH, 0.13mmol,
1.3eq). After 5 minutes, 0.013mL of benzyl bromide
(19mg, 0.11mmol, 1.1eq) was added and the mixture
stirred for 1 hour at room temperature, then added to
20mL of ethyl acetate and washed with water (2x) and
10 brine. The organic layer was removed, dried over
magnesium sulfate, filtered and solvents removed
under vacuum. The residue was purified by medium
pressure liquid chromatography on silica, eluting
with ethyl acetate/hexane (1:1) to afford 44mg
15 (0.88mmol, 90%) of product. ^1H NMR (200MHz,
 CDCl_3): 1.37 (s,3H), 1.38 (s,3H), 1.73 (m,1H),
2.3-2.6 (m,5H), 4.48 (m,1H), 4.80 (d,15Hz,1H), 5.07
(br s,2H), 5.23 (d,15Hz,1H), 5.62 (br s,1H), 6.67 (br
d,7Hz,1H), 7.1-7.4 (m,14H). FAB-MS: calculated for
20 $\text{C}_{30}\text{H}_{33}\text{N}_3\text{O}_4$ 499; found 500 ($\text{M}+\text{H}$,100%).

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-
1-(phenylmethyl)-1H-1-benzazepin-3(R)-yl]-
butanamide. trifluoroacetate

25 The intermediate obtained in Step A (17mg,
0.034mmol) dissolved in 2mL of methanol was
hydrogenated for 6 hours at room temperature and one
atmosphere over 5mg of $\text{Pd}(\text{OH})_2$ on carbon. The
mixture was filtered through Celite and the filtrate
30 concentrated under vacuum. The residue was purified
by reverse phase HPLC on C-18, eluting with
methanol/0.1% aqueous trifluoroacetic acid (linear

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gradient: 60% methanol to 80% methanol over 10 minutes) to afford 13mg (0.027mmol, 80%) of the title compound. ^1H NMR (200MHz, CD_3OD): 1.32 (s,3H), 1.35 (s,3H), 2.0-2.6 (m,6H), 4.35 (dd;7,11Hz;1H), 4.82 (d,15Hz,1H), 5.13 (d,15Hz,1H), 7.1-7.4 (m,9H). FAB-MS: calculated for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_2$ 365; found 366 ($\text{M}+\text{H}$,100%).

10

Example 4

15

2(R)-Amino-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoro-
acetate)

20

Step A 3(R)-t-Butoxycarbonylamino-2,3,4,5-tetra-
hydro-1H-1-benzazepin-2-one

25

To a solution of 400mg (2.27mmol) 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step B) in 5mL methylene chloride at room temperature was added 0.57mL (540mg, 2.48mmol, 1.1eq) of di-t-butyl dicarbonate. The mixture was stirred for 3 hours at room temperature then all volatiles were removed under vacuum to give 625mg (2.26mmol, 100%) of an oil that slowly solidified upon standing. ^1H NMR (200MHz, CDCl_3): 1.40 (s,9H), 2.00 (m,1H), 2.65 (m,2H), 2.95 (m,1H), 4.29 (m,1H), 5.42 (br d,8Hz,1H), 6.97 (d,7Hz,1H), 7.2 (m,3H), 7.50 (br s,1H).

30

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Step B 3(R)-t-Butoxycarbonylamino-2,3,4,5-tetra-
hydro-1-[2'-(N-(triphenylmethyl)-1H-tetra-
zol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-
benzazepin-2-one

To a solution of 310mg (1.12mmol) of the intermediate obtained in Step A in 2mL dry dimethylformamide at room temperature under nitrogen was added 54mg of 60% sodium hydride oil dispersion (32mg NaH, 1.3mmol, 1.2eq). After 15 minutes, a solution of 750mg (1.34mmol, 1.2eq) N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole in 2mL dry dimethylformamide was added and the mixture stirred for 2 hours. The reaction mixture was added to 50mL of ethyl acetate and washed with pH 7.0 phosphate buffer (2x) and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. Purification by medium pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (2:1), afforded 815mg (1.08mmol, 96%) of product. ^1H NMR (200MHz, CDCl_3): 1.40 (s, 9H), 1.80 (m, 1H), 2.40 (m, 3H), 4.24 (m, 1H), 4.65 (d, 15Hz, 1H), 5.08 (d, 15Hz, 1H), 5.45 (br d, 7Hz, 1H), 6.9-7.5 (m, 26H), 7.8 (m, 1H).

Step C 3(R)-Amino-1,3,4,5-tetrahydro-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one, mono(hydrochloride)

A solution of 407mg (0.54mmol) of the intermediate obtained in Step B in 5mL methanol was hydrogenated at room temperature and 1 atmosphere over 40mg of 20% $\text{Pd}(\text{OH})_2$ on carbon for 3 hours. The

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5 mixture was filtered through Celite and concentrated under vacuum to give a residue that was purified by medium pressure liquid chromatography on silica eluting with 2% methanol/ethyl acetate. The intermediate thus obtained (260mg) was dissolved in 5mL of methanol and treated with 1mL concentrated hydrochloric acid. After 16 hours, all volatiles were removed under vacuum to afford 226mg (0.51mmol, 10 94%) of product.

15 Step D 2(R)-(t-Butoxycarbonyl)amino-3-(t-butoxy)-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

20 To a suspension of 60mg (0.13mmol) of the intermediate obtained in Step C in 2mL of methylene chloride at room temperature was added 65mg (0.15mmol, 1.1eq) of BOC-D-serine t-butyl ether dicyclohexylamine salt, followed by 0.037mL of triethylamine (27mg, 0.26mmol, 2eq) and 89mg of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.20mmol, 1.5eq). After 1 hour at room temperature, all volatiles were removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with 2% methanol/ethyl acetate to afford 68mg (0.10mmol, 77%) of product. ^1H NMR (200MHz, CDCl_3): 1.15 (s, 9H), 1.32 (s, 9H), 1.88 (m, 1H), 2.54 (m, 3H), 3.36 (dd; 6, 9Hz; 1H), 3.72 (m, 1H), 4.10 (m, 1H), 4.45 (m, 1H), 4.89 (d, 15Hz, 1H), 5.05 (d, 15Hz, 1H), 5.38 (br

- 83 -

d, 7Hz, 1H), 7.00 (d, 8Hz, 2H), 7.1-7.6 (m, 9H), 7.90 (m, 1H). FAB-MS: calc. for C₃₆H₄₃N₇O₅ 653; found 654 (M+H, 8%).

5

Step E 2(R)-Amino-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

10

A solution of 65mg (0.099mmol) of the intermediate obtained in Step D in 2mL methylene chloride at room temperature was treated with 0.1mL of anisole followed by 1mL anhydrous trifluoroacetic acid. After 2 hours, all volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18 eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 55% methanol to 75% methanol over 10 minutes). to afford 54mg (0.088mmol, 89%) of the title compound. ¹H NMR (200MHz, CD₃OD): 2.10 (m, 1H), 2.2-2.7 (m, 3H), 3.93 (m, 2H), 4.38 (dd; 8, 12Hz; 1H), 4.85 (d, 14Hz, 1H), 5.29 (d, 14Hz, 1H), 7.01 (d, 8Hz, 2H), 7.1-7.4 (m, 6H), 7.5-7.7 (m, 4H). FAB-MS: calc. for C₂₇H₂₇N₇O₃ 497; found 498 (M+H, 100%).

25

Example 5

2(R)-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-pentanamide, mono(trifluoroacetate)

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Step A N-(t-butoxycarbonyl)-D-norvaline

D-Norvaline (2.0g, 17.0mmol) suspended in
5mL methylene chloride was treated with 4.3mL of
di-t-butyl-dicarbonate (4.1g, 18.7mmol, 1.1eq)
followed by 4.8mL of triethylamine (3.5g, 34mmol,
2eq). The mixture was stirred at room temperature
for 20 hours then added to 100mL ethyl acetate and
washed with 5% citric acid (2x) and brine. The
10 organic layer was removed, dried over magnesium
sulfate, filtered and solvent removed under vacuum to
afford 3.55g of the product as a clear, viscous
gum. ^1H NMR (200MHz, CDCl_3): 1.00 (t, 7Hz, 3H), 1.51
(s, 9H), 1.5-2.0 (m, 4H), 4.35 (m, 1H), 5.08 (m, 1H).

15

Step B 2(R)-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3(R)-yl]-pentan-
amide, mono(trifluoroacetate)

20

The title compound was prepared from
N-(t-butoxycarbonyl)-D-norvaline and 3(R)-amino-
1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one
hydrochloride (Example 4, Step C), using the
procedures described in Example 4, Steps D and E.
25 ^1H NMR (200MHz, CD_3OD): 0.96 (t, 7Hz, 3H), 1.45
(m, 2H), 1.80 (m, 2H), 2.0-2.6 (m, 4H), 3.81 (t, 7Hz, 1H),
4.36 (dd; 7, 11Hz; 1H), 4.8 (d, 15Hz, 1H), 5.22
(d, 15Hz, 1H), 6.96 (d, 8Hz, 2H), 7.1-7.3 (m, 6H), 7.4-7.7
(m, 4H). FAB-MS: calc. for $\text{C}_{29}\text{H}_{31}\text{N}_7\text{O}_2$ 509; found
30 510 ($\text{M}+\text{H}$, 100%).

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Example 6

2(R)-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
5 [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoro-
acetate)

The title compound was prepared from
10 N-(t-butoxycarbonyl)-D-valine and 3(R)-amino-1,3,4,5-
tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-2H-1-benzazepin-2-one hydrochloride
(Example 4, Step C), using the procedures described
in Example 4, Steps D and E. ¹H NMR (200MHz,
15 CD₃OD): 1.05 (d,7Hz,3H), 1.09 (d,7Hz,3H), 2.0-2.6
(m,5H), 3.68 (d,5Hz,1H), 4.40 (dd;7,11Hz;1H), 4.8
(d,15Hz,1H), 5.23 (d,15Hz,1H), 6.98 (d,8Hz,2H),
7.1-7.3 (m,6H), 7.4-7.7 (m,4H). FAB-MS: calc. for
C₂₉H₃₁N₇O₂ 509; found 510 (M+H,100%).

20

Example 7

2(R)-Amino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
25 1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoro-
acetate)

Step A 2(R)-t-Butoxycarbonylamino-3-phenyl-N-
[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-
30 3(R)-yl]-propanamide
To a solution of 30mg (0.17mmol) 3(R)-amino-
2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1;

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Step B) in 2mL methylene chloride at room temperature was added 50mg (0.19mmol, 1.1eq) N-(t-butoxycarbonyl)-D-phenylalanine followed by 0.047mL (34mg, 0.34mmol, 2eq) of triethylamine and 113mg (0.26mmol, 1.5eq) benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. After 2 hours at room temperature, the mixture was added to 30mL of ethyl acetate and washed with 5% citric acid (2x), saturated aqueous sodium bicarbonate and brine. The organic layer was removed, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate to afford 71mg (0.17mmol, 100%) of the product. ¹H NMR (200MHz, CDCl₃): 1.38 (s, 9H), 1.9 (m, 1H), 2.6-3.1 (m, 5H), 4.44 (m, 2H), 5.10 (br d, 7Hz, 1H), 6.95 (d, 8Hz, 1H), 7.1-7.3 (m, 8H), 8.33 (br s, 1H). FAB-MS: calc. for C₂₄H₂₉N₃O₄ 423; found 424 (M+H, 65%).

Step B 2(R)-t-Butoxycarbonylamino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-1H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yll-propanamide

To a solution of 70mg (0.17mmol) of the intermediate obtained in Step A in 0.5mL dry dimethylformamide at room temperature under nitrogen was added 8mg of 60% sodium hydride oil dispersion (5mg NaH, 0.2mmol, 1.2eq). After 10min., a solution of 120mg (0.21mmol, 1.3eq) N-triphenylmethyl-5-(4'-bromomethylbiphen-2-yl)tetrazole in 0.5mL

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dimethylformamide was added and the mixture stirred at room temperature for 1 hour. The reaction mixture was added to 30mL of ethyl acetate/hexane (1:1) and washed with pH 7.0 phosphate buffer and once with brine. The organic layer was removed, dried over magnesium sulfate filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (2:1) to afford 139mg (0.15mmol, 93%) of the product. ^1H NMR (200MHz, CDCl_3): 1.40 (s, 9H), 1.67 (m, 1H), 2.3-2.7 (m, 3H), 3.02 (d, 6Hz, 2H), 4.37 (m, 2H), 4.72 (d, 15Hz, 1H), 4.90 (br d, 1H), 5.05 (d, 15Hz, 1H), 6.9-7.5 (m, approx. 30H), 7.86 (m, 1H).

Step C 2(R)-Amino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-y1]-propanamide. mono(trifluoroacetate)

A solution of 139mg (0.15mmol) of the intermediate obtained in Step B in 5mL methanol was hydrogenated over 30mg of 20% $\text{Pd}(\text{OH})_2$ on carbon at one atmosphere for 3 hours. The mixture was filtered through Celite and the filtrate concentrated under vacuum. The residue was redissolved in 2mL methylene chloride and the solution treated with 0.1mL of anisole followed by 1mL trifluoroacetic acid. After 2 hours at room temperature, all volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol over

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10 minutes) affording 82mg (0.12mmol, 79%) of the title compound. ^1H NMR (200MHz, CD₃OD): 2.1 (m, 1H), 2.3-2.6 (m, 3H), 3.00 (dd; 9, 14Hz; 1H), 3.33 (dd; 5, 14Hz; 1H), 4.13 (dd; 5, 9Hz; 1H), 4.38 (dd; 7, 11Hz; 1H), 4.89 (d, 15Hz, 1H), 5.18 (d, 15Hz, 1H), 7.00 (d, 8Hz, 2H), 7.1-7.4 (m, 11H), 7.45-7.70 (m, 4H). FAB-MS: calc. for C₃₃H₃₁N₇O₂ 557; found 558 (M+H, 100%).

10

Example 8

15 2(R)-Amino-4-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

20 The title compound was prepared from 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1; Step B) and N-(t-butoxycarbonyl)-D-homophenylalanine by the procedures described in Example 7. ^1H NMR (200MHz, CD₃OD): 2.1 (m, 3H), 2.2-2.6 (m, 3H), 2.75 (m, 2H), 3.94 (t, 7Hz, 1H), 4.30 (dd; 7, 11Hz; 1H), 4.84 (d, 15Hz, 1H), 5.22 (d, 15Hz, 1H), 6.97 (d, 8Hz, 2H), 7.1-7.7 (m, 15H). FAB-MS: calc. for C₃₄H₃₃N₇O₂ 571; found 572 (M+H, 100%).

25

Example 9

30 2(R)-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

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The title compound was prepared from
3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one
(Example 1; Step B) and N-(t-butoxycarbonyl)-D-
5 alanine by the procedures described in Example 7.
¹H NMR (200MHz, CD₃OD): 1.51 (d,7Hz,3H), 2.0-2.6
(m,4H), 3.90 (q,7Hz,1H), 4.36 (dd;7,12Hz;1H), 4.82
(d,15Hz,1H), 5.23 (d,15Hz,1H), 6.98 (d,8Hz,2H),
7.10-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calc.
10 for C₂₇H₂₇N₇O₂ 481; found 482 (M+H,100%).

Example 10

2(S)-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-
15 tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benz-
azepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

The title compound was prepared from
3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one
(Example 1; Step B) and N-(t-butoxycarbonyl)-L-
20 alanine by the procedures described in Example 7.
¹H NMR (200MHz, CD₃OD): 1.42 (d,7Hz,3H), 2.0-2.6
(m,4H), 3.92 (q,7Hz,1H), 4.31 (dd;7,12Hz;1H), 4.88
(d,15Hz,1H), 5.19 (d,15Hz,1H), 7.00 (d,8Hz,2H),
7.10-7.35 (m,6H), 7.45-7.70 (m,4H). FAB-MS: calc.
25 for C₂₇H₂₇N₇O₂ 481; found 482 (M+H,100%).

Example 11

2(R)-Methylamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

The title compound was prepared from
3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

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(Example 1; Step B) and N-methyl-N-(t-butoxycarbonyl)-D-alanine by the procedures described in Example 7.

5 ¹H NMR (200MHz, CD₃OD): 1.52 (d, 7Hz, 3H), 2.0-2.6 (m, 4H), 2.60 (s, 3H), 3.81 (q, 7Hz, 1H), 4.36 (dd, 8, 12Hz, 1H), 4.85 (d, 15Hz, 1H), 5.22 (d, 15Hz, 1H), 6.98 (d, 8Hz, 2H), 7.10-7.35 (m, 6H), 7.45-7.70 (m, 4H). FAB-MS: calc. for C₂₈H₂₉N₇O₂ 495; found 496 (M+H, 100%).

10

Example 12

15 2(R)-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

Step A: 2(R)-(t-Butoxycarbonylamino)butanoic acid
20 (R)-2-Aminobutanoic acid (1.03g, 10.0mmol) suspended in 5mL methylene chloride was treated with 2.3mL of di-t-butyl-dicarbonate (2.18g, 10.0mmol, 1eq) and 4mL of diisopropylethylamine (2.83g, 23mmol, 2.3eq). The mixture was stirred at room temperature for 16 hours then extracted with 30mL saturated aqueous sodium bicarbonate. The aqueous layer was washed with 20mL of methylene chloride then removed and acidified to pH 2 by dropwise addition of saturated aqueous potassium hydrogen sulfate. The mixture was extracted with ethyl acetate (2x20mL); the combined extracts were dried over magnesium sulfate, filtered and solvents removed under vacuum to afford 451mg (2.2mmol, 22%) of product. ¹H NMR (200MHz, CDCl₃): 0.93 (t, 8Hz, 3H), 1.40 (s, 9H),

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1.6-2.0 (m, 2H), 4.25 (m, 1H), 5.10 (br d, 7Hz, 1H), 6.45
(br s, 1H).

5 Step B: The title compound was prepared from the intermediate obtained in Step A and 3(R)-amino-
2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1;
Step B) by the procedures described in Example 7.
10 ¹H NMR (200MHz, CD₃OD): 1.05 (t, 7Hz, 3H), 1.8-2.6
(m, 6H), 3.78 (t, 6Hz, 1H), 4.38 (m, 1H), 4.82
(d, 15Hz, 1H), 5.23 (d, 15Hz, 1H), 6.98 (d, 8Hz, 2H),
7.10-7.35 (m, 6H), 7.45-7.70 (m, 4H). FAB-MS: calc.
for C₂₈H₂₉N₇O₂ 495; found 496 (M+H, 77%).

15

Example 13

20 2(R)-Amino-3-[indol-3-yl]-N-[2,3,4,5-tetrahydro-2-oxo-
1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoro
acetate)

25 Step A 2(R)-t-Butoxycarbonylamino-3-[N-formyl-
(indol-3-yl)]-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(N-(triphenylmethyl)-1H-tetrazol-5-yl)-
[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3(R)-yl]-propanamide

30 This intermediate was prepared from
N_a-t-butoxycarbonyl-N'-formyl-D-tryptophan and
3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one
(Example 1; Step B) by the procedures described in
Example 7, Steps A and B. ¹H NMR (200MHz, CDCl₃):
1.43 (s, 9H), 2.3-2.5 (m, 4H), 3.09 (dd; 8, 13Hz; 1H),
3.28 (m, 1H), 4.4 (m, 2H), 4.73 (d, 15Hz, 1H), 4.94

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(d,15Hz,1H), 5.2 (br s,1H), 6.65 (d,7Hz,1H), 6.9-7.5
(m, approx. 30H), 7.56 (d,8Hz,1H), 7.84 (m,1H), 8.18
(br s,1H).

5

Step B: 2(R)-Amino-3-[indol-3-yl]-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]propanamide, mono(trifluoroacetate)

10

A solution of 125mg (0.13mmol) of the intermediate obtained in Step A in 2mL of methanol was hydrogenated at room temperature and one atmosphere over 30mg of 20% Pd(OH)₂ on carbon for 3 hours. The mixture was filtered through Celite and solvent removed under vacuum. The residue was redissolved in 2mL of methylene chloride and treated with 0.1mL of anisole followed by 1mL of trifluoroacetic acid. After 1 hour at room temperature, all volatiles were removed under vacuum and the residue redissolved in 2mL of methanol and treated with 0.5mL of concentrated hydrochloric acid. The mixture was heated at 60°C for 2 hours then all volatiles were removed under vacuum. The residue was purified by reverse-phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 55% methanol increased to 75% methanol over 10 minutes) to afford 68mg (0.096mmol, 74%) of the title compound. ¹H NMR (200MHz, CD₃OD): 2.0 (m,1H), 2.2-2.6 (m,3H), 3.20 (dd;8,13Hz;1H), 3.44 (dd;6,13Hz;1H), 4.14 (dd;6,8Hz;1H), 4.29 (dd;6,11Hz;1H), 4.76 (d,15Hz,1H), 5.22 (d,15Hz,1H), 6.9-7.7 (m,17H). FAB-MS: calc. for C₃₅H₃₂N₈O₂ 596; found 597 (M+H,100%).

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Example 14

5 2(R)-Amino-3-[imidazol-4-yl]-N-[2,3,4,5-tetrahydro-2-
oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono-
(trifluoroacetate)

10 Step A 2(R)-t-Butoxycarbonylamino-3-[N-tosyl-
 (imidazol-4-yl)]-N-[2,3,4,5-tetrahydro-
 2-oxo-1H-1-benzazepin-3(R)-yl]-propanamide
 Prepared from N_a-t-butoxycarbonyl-Nim-
 tosyl-D-histidine and 3(R)-amino-2,3,4,5-tetrahydro-
 1H-1-benzazepin-2-one (Example 1; Step B) by the
15 procedure described in Example 7, Step A. ¹H NMR
 (200MHz, CDCl₃): 1.38 (s,9H), 1.70 (m,1H), 2.42
 (s,3H), 2.5-2.9 (m,5H), 4.42 (m,2H), 5.77 (br s,1H),
 6.95 (d,7Hz,1H), 7.05 (s,1H), 7.1-7.3 (m,3H), 7.33
 (d,8Hz,2H), 7.58 (br d,7Hz,1H), 7.79 (d,8Hz,2H), 7.90
20 (s,1H), 8.40 (br s,1H). FAB-MS: calc. for
 C₂₈H₃₃N₅O₆S 567; found 568 (M+H,100%).

25 Step B 2(R)-t-Butoxycarbonylamino-3-[N-tosyl-
 (imidazol-4-yl)]-N-[2,3,4,5-tetrahydro-2-oxo-
 1-[[2'-[N-(triphenylmethyl)-1H-tetrazol-5-
 y1][1,1'-biphenyl]-4-yl]methyl]-1H-1-benz-
 azepin-3(R)-yl]-propanamide
 Prepared from the product obtained in Step A
 and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-
 yl)] tetrazole by the procedure described in Example
30 7, Step B. ¹H NMR (200MHz,CDCl₃): 1.43 (s,9H),
 2.2-2.4 (m,4H), 2.40 (s,3H), 2.83 (dd;5,14Hz;1H),
 3.05 (dd;6,14Hz;1H), 4.35 (m,2H), 4.63 (d,14Hz,1H),

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5.12 (d,14Hz,1H), 5.88 (br s,1H), 6.9-7.5 (m,approx.
28H), 7.75-7.95 (m,4H).

5 Step C: 2(R)-Amino-3-[imidazol-4-yl]-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-
y1)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benz-
azepin-3(R)-yl]-propanamide, mono(trifluoro-
acetate)

10 A solution of 104mg (0.10mmol) of the
intermediate obtained in Step B in 2mL of chloroform
at room temperature was treated with 27mg (0.20mmol,
2eq) of 1-hydroxybenzotriazole hydrate. After 14
hours, the solvent was removed under vacuum and the
residue redissolved in 2mL of methanol and
15 hydrogenated at one atmosphere over 20mg of 20%
 $Pd(OH)_2/C$ for 3 hours. The mixture was filtered
through Celite and solvent removed under vacuum. The
residue was redissolved in 2mL of methylene chloride
and treated with 0.1mL of anisole followed by 1mL of
20 trifluoroacetic acid. After 2 hours at room
temperature, all volatiles were removed under vacuum
and the residue purified by reverse-phase HPLC on
C-18, eluting with methanol/0.1% aqueous
trifluoroacetic acid (linear gradient: 45% methanol
25 increased to 65% methanol over 10 minutes) to afford
56mg (0.085mmol, 85%) of the title compound. 1H NMR
(200MHz, CD_3OD): 2.15-2.50 (m,4H), 3.38
(dd;6,12Hz;1H), 3.51 (dd;4,12Hz;1H), 4.24
(dd;4,6Hz;1H), 4.38 (dd;8,12Hz;1H), 5.12 (s,2H), 7.03
30 (d,8Hz,2H), 7.2-7.4 (m,6H), 7.4-7.7 (m,5H), 8.61
(s,1H). FAB-MS: calc. for $C_{30}H_{29}N_9O_2$ 547; found
548 ($M+H$,77%).

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Example 15

5 2(S)-Amino-3-[imidazol-4-yl]-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono-(trifluoroacetate)

The title compound was prepared from N_a-t-butoxycarbonyl-N_{im}-tosyl-L-histidine, dicyclohexylamine salt and 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1; Step B) by the procedures described in Example 14. ¹H NMR (200MHz, CD₃OD): 1.9-2.6 (m,4H), 3.25 (m,2H), 4.16 (t,7Hz,1H), 4.31 (dd;7,11Hz;1H), 4.88 (d,15Hz,1H), 5.17 (d,15Hz,1H), 6.99 (d,8Hz,2H), 7.1-7.6 (m,11H), 8.82 (s,1H). FAB-MS: calc. for C₃₀H₂₉N₉O₂ 547; found 548 (M+H,81%).

Example 16

20 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-methyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

25 Step A: 3-(t-Butoxycarbonylamino)-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

30 A solution of 50mg (0.080mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) in

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2mL of methylene chloride at room temperature was treated with 0.017mL of triethylamine (12mg, 0.12mmol, 1.5eq) followed by 0.021mL of di-t-butyl-dicarbonate (20mg, 0.091mmol, 1.1eq). The mixture was stirred for 14 hours then all volatiles were removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate/acetonitrile/methanol (9:1:.5) to afford 42mg of product (0.069mmol, 86%). ^1H NMR (200MHz, CD_3OD): 1.25 (s, 6H), 1.45 (s, 9H), 2.0 (m, 1H), 2.2-2.6 (m, 5H), 4.32 (m, 1H), 4.78 (d, 14Hz, 1H), 5.26 (d, 14Hz, 1H), 6.97 (d, 8Hz, 2H), 7.10-7.35 (m, 6H), 7.40-7.60 (m, 4H). FAB-MS: calculated for $\text{C}_{34}\text{H}_{39}\text{N}_7\text{O}_4$ 609; found 610 ($\text{M}+\text{H}$, 22%).

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-methyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

A solution of 42mg (0.070mmol) of the intermediate obtained in Step A in 2mL of methylene chloride at room temperature was treated with a diethyl ether solution of diazomethane until a yellow color persisted. Glacial acetic acid (0.2mL) was added and all volatiles removed under vacuum. The residue was redissolved in 2mL of methylene chloride and treated with 0.1mL of anisole followed by 0.5mL of trifluoroacetic acid. After two hours at room temperature, all volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient; 75% methanol

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increased to 85% methanol over ten minutes). Two components were isolated: the title compound elutes first and 26mg (0.041mmol, 59%) was thus obtained.

5 This was followed by the N₂ isomer (8mg, 0.013mmol, 18%) described in Example 17. ¹H NMR (200MHz, CD₃OD): 1.33 (s,3H), 1.37 (s,3H), 2.0-2.6 (m,6H), 3.13 (s,3H), 4.34 (dd;7,11Hz;1H), 4.77 (d,14Hz,1H), 5.37 (d,14Hz,1H), 6.98 (d,8Hz,2H), 7.1-7.4 (m,6H), 10 7.5-7.8 (m,4H). FAB-MS: calc. for C₃₀H₃₃N₇O₂ 523; found 524 (M+H,100%).

Example 17

15 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(2-methyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

The title compound was obtained from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) by the procedures described in Example 16. ¹H NMR (200MHz, CD₃OD): 1.32 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 4.21 (s,3H), 4.37 (dd;8,12Hz;1H), 4.87 (d,15Hz,1H), 5.22 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.6 (m,9H), 7.69 (d,8Hz,1H). FAB-MS: calc. for C₃₀H₃₃N₇O₂ 523; found 524 (M+H,100%).

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Example 18

5 3-(2-Benzylxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono-(trifluoroacetate)

To a stirred solution of 50mg (0.080mmol)
10 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate
15 (Example 1) in 3mL of absolute methanol was added 0.022mL (16mg, 0.16mmol, 2eq) of triethylamine followed by 120mg of powdered 3A molecular sieves.
20 To this stirred mixture was added a solution of 0.012mL (12mg, 0.08mmol, 1eq) of benzyloxyacetaldehyde (prepared from 2,3-O-isopropylideneglycerol by the method of Shiao, et al, Synth. Comm., 18, 359 (1988)) in 2mL dry methanol. The pH of the reaction mixture was adjusted to 7.5 (paper) by the addition of triethylamine and trifluoroacetic acid and was stirred for two hours. To this was added 0.48mL of a 1M solution of sodium cyanoborohydride in tetrahydrofuran (0.48mmol, 6eq). The reaction mixture was stirred at room temperature for 24 hours then filtered and the filtrate treated with 2mL of glacial acetic acid. After concentration under vacuum, the residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol in 10 minutes) to afford 35mg (0.046mmol, 58%) of the title compound. ¹H NMR (200MHz, CD₃OD): 1.34 (s,3H), 1.36 (s,3H), 2.0-2.6

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(m,6H), 3.20 (t,5Hz,2H), 3.70 (t,5Hz,2H), 4.38
(dd;7,11Hz;1H), 4.52 (s,2H), 4.93 (d,15Hz,1H), 5.11
(d,15Hz,1H), 6.98 (d,8Hz,2H), 7.1-7.3 (m,11H),
5 7.4-7.6 (m,4H). FAB-MS: calc. for C₃₈H₄₁N₇O₃ 643;
found 644 (M+H,100%).

Example 19

10 3-(2-hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-
4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,
trifluoroacetate

A solution of 12mg (0.016mmol) of 3-(2-
15 benzyloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-
2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
trifluoroacetate (Example 18) in 12mL of absolute
methanol was hydrogenated at room temperature and
20 40psi over 30% Pd/C for 24 hours. The mixture was
filtered through Celite and the filtrate concentrated
under vacuum. The residue was purified by reverse
phase HPLC on C-18, eluting with methanol/0.1%
aqueous trifluoroacetic acid (linear gradient: 60%
25 methanol increased to 80% methanol in 10 minutes) to
afford 6.3mg (0.0094mmol, 59%) of the title
compound. ¹H NMR (200MHz, CD₃OD): 1.35 (s,3H),
1.38 (s,3H), 2.0-2.6 (m,6H), 3.09 (t,5Hz,2H), 3.73
(t,5Hz,2H), 4.33 (dd;7,11Hz;1H), 4.90 (d,15Hz,1H),
30 5.13 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.1-7.4 (m,6H),
7.5-7.7 (m,4H). FAB-MS: calculated for C₃₁H₃₅N₇O₃
553; found 554 (M+H,100%).

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Example 20

5 3-(2-Hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(1-(2-hydroxyethyl)-tetrazol-5-
y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-
y1]-butanamide, mono(trifluoroacetate)

10 Step A: 3-(2-Benzylloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-(2-hydroxyethyl)-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, mono(trifluoroacetate) and
15 3-(2-Benzylloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(2-(2-hydroxyethyl)-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, mono(trifluoroacetate)

20 To a solution of 40mg (0.053mmol) of 3-(2-benzylloxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]-methyl]-1H-1-benzazepin-3(R)-y1]-butanamide mono(trifluoroacetate) (Example 18) in 3mL of methanol was added a catalytic amount of pyridinium p-toluenesulfonate. Ethylene oxide was bubbled through the solution for five minutes; the flask was capped tightly and the solution stirred at room temperature for 24 hours. All volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 85% methanol in 10 minutes) to afford 18mg (0.022mmol, 42%) of the N₁ product followed by 6mg (0.0075mmol, 14%) of the N₂

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product. ^1H NMR (200MHz, CD_3OD): 1.35 (s, 3H), 1.38 (s, 3H), 2.0-2.6 (m, 6H), 3.22 (t, 5Hz, 2H), 3.54 (m, 4H), 3.71 (t, 5Hz, 2H), 4.37 (dd; 7, 11Hz; 1H), 4.55 (s, 2H), 4.86 (d, 15Hz, 1H), 5.22 (d, 15Hz, 1H), 6.95 (d, 8Hz, 2H), 7.1-7.4 (m, 11H), 7.5-7.8 (m, 4H). FAB-MS: calc. for $\text{C}_{40}\text{H}_{45}\text{N}_7\text{O}_4$ 687; found 688 ($\text{M}+\text{H}$, 100%).

Step B: 3-(2-Hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[(2'-(1-(2-hydroxyethyl)-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono-(trifluoroacetate)

A solution of 18mg (0.022mmol) of the N1 intermediate obtained in Step A in methanol was hydrogenated at room temperature and 40psi over 30% Pd/C for 24 hours. The mixture was filtered and concentrated under vacuum. The residue was purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 55% methanol increased to 85% methanol in 10 minutes) to afford 12mg (0.017mmol, 75%) of the title compound. ^1H NMR (200MHz, CD_3OD): 1.35 (s, 3H), 1.38 (s, 3H), 2.0-2.6 (m, 6H), 3.09 (t, 5Hz, 2H), 3.56 (br s, 4H), 3.73 (t, 5Hz, 2H), 4.32 (dd; 8, 12Hz; 1H), 4.81 (d, 15Hz, 1H), 5.28 (d, 15Hz, 1H), 7.00 (d, 8Hz, 2H), 7.1-7.3 (m, 6H), 7.-7.7 (m, 4H). FAB-MS: calc. for $\text{C}_{33}\text{H}_{39}\text{N}_7\text{O}_4$ 597; found 598 ($\text{M}+\text{H}$, 100%).

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Example 21

5 3-(2-Hydroxyethyl)amino-3-methyl-N-[2,3,4,5-tetra-
 hydro-2-oxo-1-[[2'-[2-(2-hydroxyethyl)-tetrazol-5-
 y1][1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-
3(R)-y1]-butanamide, mono(trifluoroacetate)

10 Step A: 3-(2-Benzylxyethyl)amino-3-methyl-N-
 [2,3,4,5-tetrahydro-2-oxo-1-[[2'-[2-(2-
 hydroxyethyl)-tetrazol-5-y1][1,1'-biphenyl]-
 4-y1]methyl]-1H-1-benzazepin-3(R)-y1]-butan-
amide, mono(trifluoroacetate)

15 Prepared from 3-(2- benzyloxyethyl)amino-3-
 methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[1H-tetra-
 zol-5-y1][1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-
 3(R)-y1]-butanamide, mono(trifluoroacetate) (Example
 18) by the procedures described in Example 20, Step
 A. ¹H NMR (200MHz, CD₃OD): 1.32 (s,3H), 1.36
20 (s,3H), 2.0-2.7 (m,6H), 3.19 (t,5Hz,2H), 3.66
 (t,5Hz,2H), 3.88 (t,5Hz,2H), 4.40 (dd;8,12Hz;1H),
 4.50 (s,2H), 4.56 (t,5Hz,2H), 5.02 (br s,2H), 6.99
 (d,8Hz,2H), 7.1-7.6 (m,15H). FAB-MS: calc. for
 C₄₀H₄₅N₇O₄ 687; found 688 (M+H,100%).

25 Step B: 3-(2-Hydroxyethyl)amino-3-methyl-N-[2,3,4,5-
 tetrahydro-2-oxo-1-[[2'-[2-(2-hydroxyethyl)-
 tetrazol-5-y1][1,1'-biphenyl]-4-y1]methyl]-
 1H-1-benzazepin-3(R)-y1]-butanamide, mono-
 (trifluoroacetate)

30 The title compound was prepared from the
 intermediate obtained in Step A by the procedure
 described in Example 20, Step B. ¹H NMR (200MHz,

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CD₃OD): 1.34 (s,3H), 1.37 (s,3H), 2.0-2.7 (m,6H),
3.08 (t,5Hz,2H), 3.72 (t,5Hz,2H), 3.90 (t,5Hz,2H),
4.35 (dd;8,12Hz;1H), 4.59 (t,5Hz,2H), 4.96
5 (d,15Hz,1H), 5.10 (d,15Hz,1H), 7.02 (d,8Hz,2H),
7.1-7.7 (m,10H). FAB-MS: calc. for C₃₃H₃₉N₇O₄
597; found 598 (M+H, 67%).

Example 22

10

3-(2-Hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono-(trifluoroacetate)

15

Step A: 3-(2-Benzylloxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono-(trifluoroacetate)

20

This intermediate was prepared as a mixture of diastereomers (at the carbinol carbon) from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) and (+/-) 2-benzylloxypropionaldehyde [prepared from 3-buten-2-ol by the method of Shiao, et al., Synth. Comm., 18, 359 (1988)] by the procedure described in Example 18, Step A.

25

¹H NMR (200MHz, CD₃OD): 1.24 (m,3H), 1.34 (m,6H), 2.0-2.6 (m,6H), 2.93 (dd;9,12Hz;1H), 3.16 (dd;3,12Hz;1H), 3.80 (m,1H), 4.40 (m,2H), 4.62 (m,2H), 4.8-5.2 (m,2H), 6.9-7.6 (m,17H). FAB-MS: calc. for C₃₉H₄₃N₇O₃ 657; found 658 (M+H,100%).

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Step B: 3-(2-Hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

5

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 19. ^1H NMR (200MHz, CD₃OD): 1.20 (d, 7Hz, 3H), 1.35 (m, 6H), 2.0-2.7 (m, 6H), 2.75 (m, 1H), 3.07 (dd; 3, 12Hz; 1H), 3.91 (m, 1H), 4.33 (dd; 8, 12Hz; 1H), 4.9 (m, 1H), 5.2 (m, 1H), 7.02 (d, 8Hz, 2H), 6.9-7.6 (m, 12H). FAB-MS: calc. for C₃₂H₃₇N₇O₃ 567; found 568 (M+H, 100%).

10

15

Example 23

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-(2-hydroxyethyl)-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

20

Step A: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-(2-hydroxyethyl)-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(trifluoroacetate)

25

To a solution of 54mg (0.099mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide mono(trifluoroacetate) (Example 1) in 2mL of methylene chloride was added a catalytic amount of pyridinium p-toluenesulfonate. Ethylene oxide was bubbled through the solution for five minutes; the flask was capped tightly and the

30

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solution stirred at room temperature for 24 hours. All volatiles were removed under vacuum and the residue purified by reverse phase HPLC on C-18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol increased to 80% methanol in 10 minutes) to afford 37mg (0.055mmol, 56%) of the title compound followed by 15mg (0.022mmol, 22%) of the N2 product. ^1H NMR (200MHz, CD₃OD): 1.32 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 3.55 (m,4H), 4.33 (dd;7,11Hz;1H), 4.79 (d,14Hz,1H), 5.31 (d,14Hz,1H), 6.99 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.5-7.8 (m,4H). FAB-MS: calc. for C₃₁H₃₅N₇O₃ 553; found 554 (M+H,100%).

15

Example 24

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[2-(2-hydroxyethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono-(trifluoroacetate)

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide mono(trifluoroacetate) (Example 1) by the procedure described in Example 23. ^1H NMR (200MHz, CD₃OD): 1.33 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 3.90 (t,5Hz,2H), 4.37 (dd;8,12Hz;1H), 4.60 (d,5Hz,2H), 4.91 (d,15Hz,1H), 5.17 (d,15Hz,1H), 7.01 (d,8Hz,2H), 7.1-7.6 (m,9H), 7.75 (d,7Hz,1H). FAB-MS: calc. for C₃₁H₃₅N₇O₃ 553; found 554 (M+H,100%).

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Example 25

5 2-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetra-
zol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3-yl]-acetamide, hydrochloride

10 Step A: 3-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
hydro-2-oxo-1H-1-benzazepin-3-yl]-acetamide

15 To a solution of 169mg (0.965 mmol) of
N-(t-butoxycarbonyl) glycine in 2mL of methylene
chloride at room temperature was added 222mg (1.158
mmol, 1.2eq) of 1-(3-dimethylaminopropyl)-3-ethyl-
carbodiimide hydrochloride, 11mg (0.09mmol, 0.1eq) of
20 4-dimethylaminopyridine and 170mg (0.97 mmol, 1eq) of
3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one
(Example 1, Step A). The reaction was stirred at
room temperature for 3 hours. The reaction was then
quenched by the addition of 5mL of 1M aqueous
hydrochloric acid, and the aqueous phase extracted
with methylene chloride (2x5mL). The combined
organic phases were dried over magnesium sulfate,
filtered and the solvent removed under vacuum. The
residue was purified by flash chromatography on
silica gel, eluting with ethyl acetate, to afford
25 218mg (0.65mmol, 68%) of the product. ¹H NMR
(200MHz, CDCl₃): 1.43 (s, 9H), 1.96 (m, 1H), 2.83
(m, 3H), 3.81(dq; 2, 8Hz; 2H), 4.54 (m, 1H), 5.21
(t, 3Hz, 1H), 7.15 (m, 4H), 7.84 (br s, 1H). FAB-MS:
30 calculated for C₁₇H₂₃N₃O₄ 333; found 334 (M+H, 43%).

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5 Step B: 2-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(N-(triphenylmethyl)-
tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3-yl]-acetamide

10 Prepared from the intermediate obtained in
Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-
biphen-4-yl)] tetrazole by the procedure described in
Example 1, Step K. ^1H NMR (200MHz, CDCl_3): 1.26
15 (s, 9H), 1.81 (m, 1H), 2.48 (m, 3H), 3.80 (dq; 3, 9Hz; 2H),
4.50 (m, 1H), 4.72 (d, 7Hz, 1H), 5.10 (d, 7Hz, 1H),
6.9-7.6 (m, 26H), 7.96 (m, 1H).

15 Step C: 2-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-
acetamide

20 323mg (0.43mmol) of the intermediate
obtained in Step B was dissolved in 1mL of glacial
acetic acid and 1mL of water was added dropwise with
stirring. The reaction mixture was stirred at room
temperature for 16 hours then solvents were removed
under vacuum and the residue purified by flash
chromatography on a silica gel column, eluting with
25 ethyl acetate to afford 109mg (0.196mmol, 46%) of the
product. ^1H NMR (200MHz, CDCl_3): 1.38 (s, 9H), 1.97
(m, 1H), 2.55 (m, 3H), 3.65 (m, 2H), 4.50 (m, 1H), 4.85
(d, 15Hz, 1H), 5.05 (d, 16Hz, 1H), 5.51 (br s, 1H)
6.95-7.95 (m, 11H), 7.83 (d, 3Hz, 1H).

30 Step D: 2-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(
1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3-yl]-acetamide,
hydrochloride

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The intermediate obtained in Step C (109mg, 0.196mmol) was dissolved in 2mL of methanol and treated with 0.1mL of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature for 16 hours then solvents were removed under vacuum and the residue redissolved in water and washed with ethyl acetate. The aqueous layer was separated and the solvent removed under vacuum to yield 87mg (0.17mmol, 88%) of the title compound.

¹H NMR (200MHz, CD₃OD): 2.10 (m, 1H), 2.48 (m, 3H), 3.68 (s, 2H), 4.37 (m, 1H), 4.84 (d, 14Hz, 1H), 5.22 (d, 14Hz, 1H), 6.9-7.7 (m, 12H). FAB-MS: calculated for C₂₆H₂₅N₇O₂ 467; found 468 (M+H, 100%).

15

EXAMPLE 26

4-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetra-
zol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3-yl]butanamide, hydrochloride

20

25

30

Step A: 4-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
hydro-2-oxo-1H-1-benzazepin-3-yl]butanamide

Prepared from 3-amino-2,3,4,5-tetrahydro-1H-

[1]benzazepin-2-one (Example 1, Step A) and 4-(t-

butoxycarbonylamino)butyric acid by the procedure

described in Example 25, Step A. ¹H NMR (200MHz,

CDCl₃): 1.42 (s, 9H), 1.7-2.1 (m, 3H), 2.24

(t, 5Hz, 2H), 2.58-3.29 (m, 5H), 4.57 (m, 1H), 4.86 (br

s, 1H), 7.0-7.3 (m, 4H), 8.32 (s, 1H). FAB-MS:

calculated for C₁₉H₂₇N₃O₄ 361; found 362 (M+H, 60%).

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5 Step B: 4-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
 hydro-2-oxo-1-[[2'-(N-(triphenylmethyl)-
 tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3-yl]-butanamide

10 Prepared from the intermediate obtained in
Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-
biphen-4-yl)] tetrazole by the procedure described in
Example 1, Step K. ^1H NMR (200MHz, CDCl_3): 1.42
(s, 9H), 1.78 (m, 3H), 2.20 (t, 5Hz, 2H), 2.2-2.7 (m, 2H),
3.13 (m, 2H), 4.46 (m, 1H), 4.70 (d, 14Hz, 1H), 5.10
(d, 14Hz, 1H), 6.64 (d, 7Hz, 1H), 6.8-7.5 (m, 26H), 7.85
(m, 1H).

15 Step C: 4-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
 hydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
 biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-
butanamide

20 The intermediate obtained in Step B (349mg,
0.40mmol) was dissolved in 5mL of methanol and
hydrogenated at room temperature and one atmosphere
over 70mg of 20% $\text{Pd}(\text{OH})_2/\text{C}$ for 16 hours. The
reaction mixture was filtered through Celite and
solvent removed under vacuum. The crude product was
25 purified by flash chromatography on silica, eluting
with 10% methanol/ethyl acetate to afford 168mg
(0.28mmol, 71%) of product. ^1H NMR (200MHz,
 CD_3OD): 1.41 (s, 9H), 1.72 (m, 2H), 2.0-2.6 (m, 6H),
3.24 (t, 7Hz, 2H), 4.32 (m, 1H), 4.85 (d, 14Hz, 1H), 5.20
30 (d, 14Hz, 1H), 6.9-7.7 (m, 12H).

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Step D: 4-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

5

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 25, Step D. ^1H NMR (200MHz, CD₃OD): 1.8-2.6 (m, H), 2.96 (t, 6Hz, 2H), 4.30 (m, 1H), 4.88 (d, 15Hz, 1H), 5.25 (d, 15Hz, 1H), 6.9-7.4 (m, 8H), 7.5-7.7 (m, 4H). FAB-MS: calculated for C₂₈H₂₉N₇O₂ 495; found 496 (M+H, 100%).

10

Example 27

15

2-Amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-propanamide, hydrochloride

20

Step A: 2-(t-Butoxycarbonylamino)-2-methyl-N-[2,3,4,-5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-propanamide

25

Prepared from 2-(t-butoxycarbonylamino)-2-methylpropanoic acid and 3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step A) by the procedure described in Example 25, Step A. ^1H NMR (200MHz, CDCl₃): 1.38 (s, 12H), 1.44 (s, 3H), 1.90 (m, 1H), 2.5-3.0 (m, 3H), 4.45 (m, 1H), 5.10 (s, 1H), 6.97 (m, 1H), 7.20 (m, 3H), 8.45 (s, 1H).

30

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Step B: 2-(t-Butoxycarbonylamino)-2-methyl-N-[2,3,4,-
5-tetrahydro-2-oxo-1-[[2'-(N-(triphenyl-
methyl)-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3-yl]-propanamide

5

Prepared from the intermediate obtained in
Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-
biphen-4-yl)] tetrazole by the procedure described in
Example 1, Step K. ^1H NMR (200MHz, CDCl_3): 1.42
10 (s, 9H), 1.43 (s, 3H), 1.47 (s, 3H), 1.75 (m, 1H),
2.2-2.7 (m, 3H), 4.45 (m, 1H), 4.71 (d, 14Hz, 1H), 5.10
(d, 14Hz, 1H), 6.9-7.5 (m, 26H), 7.87 (m, 1H).

15

Step C: 2-(t-butoxycarbonylamino)-2-methyl-N-[2,3,4,-
5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-
[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3-yl]-propanamide

Prepared from the intermediate obtained in
Step B by the procedure described in Example 26, Step
20 C. ^1H NMR (200MHz, CD_3OD): 1.34 (s, 6H), 1.40
(s, 9H), 1.95 (m, 1H), 2.44 (m, 3H), 4.30 (m, 1H), 4.77
(d, 14Hz, 1H), 5.26 (d, 14Hz, 1H), 6.9-7.7 (m, 12H).
FAB-MS: calculated for $\text{C}_{33}\text{H}_{37}\text{N}_7\text{O}_4$ 595; found 596
(M+H, 40%).

25

Step D: 2-Amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-
1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3-yl]-propanamide,
hydrochloride

30

The title compound was prepared from the
intermediate obtained in Step C by the procedure
described in Example 25, Step D. $^1\text{H-NMR}$ (200MHz,
 CD_3OD): 1.50 (s, 3H), 1.62 (s, 3H), 2.2-2.7 (m, 4H),

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4.32 (m, 1H), 4.85 (d, 14Hz, 1H), 5.17 (d, 14Hz, 1H),
6.9-7.7 (m, 12H). FAB-MS: calculated for C₂₈H₂₉N₇O₂
495; found 496 (M+H, 100%).

5

Example 28

10

6-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetra-
zol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3-yl]-hexanamide, hydrochloride

15

Step A: 6-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
hydro-2-oxo-1H-1-benzazepin-3-yl]-hexanamide
Prepared from 6-(t-butoxycarbonylamino)-
hexanoic acid and 3-amino-2,3,4,5-tetrahydro-1H-
[1]benzazepin-2-one (Example 1, Step A) by the
procedure described in Example 25, Step A. ¹H NMR
(200 MHz, CDCl₃): 1.2-1.7 (m, 14H), 1.92 (m, 2H), 2.16
(t, 5Hz, 2H), 2.5-3.1 (m, 6H), 4.53 (m, 2H), 6.54
(d, 7Hz, 1H), 6.96 (m, 1H), 7.18 (m, 3H), 8.00 (s, 1H).
FAB-MS: calculated for C₂₁H₃₁N₃O₄ 389; found 390
(M+H, 18%).

20

25

Step B: 2-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(N-(triphenylmethyl)-
tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3-yl]-hexanamide

30

Prepared from the intermediate obtained in
Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-
biphen-4-yl)] tetrazole by the procedure described in
Example 1, Step K. ¹H NMR (200MHz, CDCl₃): 1.1-1.9

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(m, 16H), 2.15 (t, 5Hz, 2H), 2.2-2.7 (m, 3H), 3.07
5 (q, 6Hz, 2H), 4.49 (m, 2H), 4.70 (d, 14Hz, 1H), 5.11
(d, 14Hz, 1H), 6.49 (d, 8Hz, 1H), 6.8-7.5 (m, 26H), 7.86
(m, 1H).

Step C: 2-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
10 hydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-
hexanamide

Prepared from the intermediate obtained in
Step B by the procedure described in Example 26, Step
C. ^1H NMR (200MHz, CD₃OD): 1.1-1.7 (m, 16H),
2.0-2.6 (m, 5H), 2.98 (t, 2H), 4.32 (m, 1H), 4.81
15 (d, 16Hz, 1H), 5.22 (d, 16Hz, 1H), 6.95 (m, 2H), 7.23
(m, 6H), 7.52 (m, 4H). FAB-MS: calculated for
C₃₅H₄₁N₇O₄ 623; found 646 (M+Na, 45%).

Step D: 2-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(
1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
20 methyl]-1H-1-benzazepin-3-yl]-hexanamide,
hydrochloride

The title compound was prepared from the
intermediate obtained in Step C by the procedure
described in Example 25, Step D. ^1H NMR (200MHz,
25 CD₃OD): 1.88 (m, 2H), 1.63 (m, 4H) 2.0-2.7 (m, 6H),
2.90 (br s, 2H), 4.31 (m, 1H), 4.86 (d, 14Hz, 1H), 5.17
(d, 14Hz, 1H), 6.98 (d, 8Hz, 2H), 7.22 (m, 6H), 7.56
(m, 4H). FAB-MS: calculated for C₃₀H₃₃N₇O₂ 523;
found 524 (M+H, 100%).

30

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Example 29

5 1-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetra-
zol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3-yl]-cyclohexanecarboxamide, hydrochloride

10 Step A: 1-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
hydro-2-oxo-1H-1-benzazepin-3-yl]-cyclo-
hexanecarboxamide

15 Prepared from 1-(t-butoxycarbonylamino)-
cyclohexanecarboxylic acid and 3-amino-2,3,4,5-
tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step A)
by the procedure described in Example 25, Step A. ¹H
NMR (200MHz, CDCl₃): 1.1-2.2 (m,19H), 2.00 (m,2H),
2.50 (m,2H), 4.55 (m,1H), 6.9-7.2 (m,4H). FAB-MS:
calculated for C₂₂H₃₁N₃O₄ 401; found 402 (M+H,40%).

20 Step B: 1-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(N-(triphenylmethyl)-
tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3-yl]-cyclohexanecarboxamide

25 Prepared from the intermediate obtained in
Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-
biphen-4-yl)] tetrazole by the procedure described in
Example 1, Step K. ¹H NMR (200MHz, CDCl₃): 1.1-2.1
(m,19H), 2.20 (m,4H), 4.45 (m,1H), 4.67 (s,1H), 4.72
(d,13Hz,1H), 5.06 (d,13Hz,1H), 6.8-7.5 (m,26H), 7.86
(m,1H).

30 Step C: 1-t-Butoxycarbonylamino-N-[2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-
cyclohexanecarboxamide

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Prepared from the intermediate obtained in Step B by the procedure described in Example 26, Step C. ^1H NMR (200MHz, CD_3OD): 1.2-1.9 (m, 19H), 2.00 (br s, 2H), 2.53 (m, 3H), 4.40 (m, 1H), 4.86 (d, 14Hz, 1H), 5.34 (d, 14Hz, 1H), 6.81 (br s, 1H), 7.0-7.5 (m, 8H), 7.60 (m, 4H). FAB-MS: calculated for $\text{C}_{36}\text{H}_{41}\text{N}_7\text{O}_4$ 635; found 636 ($\text{M}+\text{H}$, 20%).

10 Step D: 1-Amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-cyclohexane-carboxamide, hydrochloride

15 The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 25, Step D. ^1H NMR (200MHz, CD_3OD): 1.6-2.4 (m, 8H), 2.28 (m, 4H), 2.62 (m, 2H), 4.42 (m, 1H), 4.96 (d, 15Hz, 1H), 5.26 (d, 15Hz, 1H), 7.0-7.5 (m, 8H), 7.64 (m, 4H). FAB-MS: calculated for $\text{C}_{31}\text{H}_{33}\text{N}_7\text{O}_2$ 535; found 536 ($\text{M}+\text{H}$, 100%).

Example 30

25 2(S),6-Diamino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-hexanamide, dihydrochloride

30 Step A: 2(S),6-Di-(t-butoxycarbonylamino)-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-hexanamide

Prepared from N_a,N_e -di(t-butoxycarbonyl)-L-lysine and 3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step A) by the procedure

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described in Example 25, Step A. ^1H NMR (200MHz, CDCl₃): 1.2-2.1 (m, 24H), 2.6-3.3 (m, 6H), 4.20 (m, 1H), 4.62 (m, 2H), 5.26 (m, 1H), 7.0-7.4 (m, 4H).
5 FAB-MS: calculated for C₂₆H₄₀N₄O₆ 504; found 505 (M+H, 20%).

10 Step B: 2(S),6-Di-(t-butoxycarbonylamino)-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-hexanamide
Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CDCl₃): 1.42 (s, 18H), 1.60 (m, 2H), 1.79 (m, 2H), 2.42 (m, 4H), 3.10 (m, 4H), 4.09 (m, 1H), 4.42 (m, 1H), 4.60 (d, 13Hz, 1H), 5.17 (d, 13Hz, 1H), 6.8-7.5 (m, 26H), 7.85 (m, 1H).

20 Step C: 2(S),6-Di-(t-butoxycarbonylamino)-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-hexanamide
Prepared from the intermediate obtained in Step B by the procedure described in Example 26, Step C. ^1H NMR (200MHz, CD₃OD): 1.0-1.8 (m, 20H), 2.00 (m, 2H), 3.00 (m, 2H), 3.95 (m, 1H), 4.32 (m, 1H), 4.76 (d, 13Hz, 1H), 5.26 (d, 13Hz, 1H), 6.9-7.4 (m, 8H), 7.4-7.6 (m, 4H). FAB-MS: calculated for C₄₀H₅₀N₈O₆ 738; found 739 (M+H, 10%).

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Step D: 2(S),6-diamino-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3-yl]-hexanamide,
dihydrochloride

5

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 25, Step D. ¹H NMR (200MHz, CD₃OD): 1.3-2.0 (m,6H), 2.0-2.7 (m,4H), 2.95 (m,2H), 10 3.95 (m,1H), 4.37 (m,1H), 4.89 (d,15Hz,1H), 5.19 (dd;4,15Hz,1H), 6.9-7.4 (m,8H), 7.5-7.7 (m,4H). FAB-MS: calculated for C₃₀H₃₄N₈O₂ 538; found 539 (M+H,100%).

15

Example 31

3-amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

20

Step A: 7-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Sodium azide 1.1g (16.92mmol) was added to a mixture of 6.0mL of chloroform and 1.1mL of water at 25 0°C. Concentrated sulfuric acid (0.44mL) was added dropwise and the mixture stirred at 0°C for two hours then filtered. The chloroform layer containing hydrazoic acid was added to a solution of 1.3g (7.92mmol) of 6-fluoro-1-tetralone (prepared by the method of Allinger and Jones, J. Org. Chem., 27, 30 70-76 (1962)) in 4.8mL of chloroform. Additional sulfuric acid (2.16mL) was added dropwise with stirring while maintaining the temperature below

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40°C. The mixture was stirred at 40°C for two hours then at room temperature for 16 hours. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was added to ice; the resulting precipitate was extracted with methylene chloride (5x). The combined extracts were washed with brine, dried over magnesium sulfate and filtered through a silica plug. Solvents were removed under vacuum to afford 162mg (0.92mmol, 11%) of the product. ^1H NMR (300MHz, CDCl_3): 2.21 (m, 2H), 2.32 (t, 7Hz, 2H), 2.77 (t, 7Hz, 2H), 6.93 (m, 3H), 7.8 (br s, 1H). FAB-MS: calculated for $\text{C}_{10}\text{H}_{10}\text{FNO}$ 179; found 180 ($\text{M}+\text{H}$, 100%).

Step B: 3-iodo-7-fluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one
7-fluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (411mg, 2.3mmol) (Step A) dissolved in a mixture of 7.9mL of dry methylene chloride and 1.0mL of dry tetrahydrofuran was treated with 1.62mL (1.18g, 11.6mmol, 5eq) of triethylamine and the resulting solution cooled to -15°C. Iodotrimethylsilane (0.66mL, 932mg, 4.7mmol, 2eq) was added followed by 1.183g of iodine (4.7mmol, 2eq) added in small portions over 5 minutes. The mixture was warmed to room temperature over 5 minutes at which time 15mL of methylene chloride was added followed by 20mL of 10% aqueous sodium sulfite. The layers were separated and the organic layer washed with 10% sodium sulfite (3x20mL). The aqueous layer was further extracted with 20mL of methylene chloride. The combined extracts were washed with

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brine, dried over magnesium sulfate, filtered and concentrated to dryness under vacuum. The crude product was chromatographed on silica gel, eluting with methylene chloride/methanol (99:1) to afford 511mg (1.68mmol, 73%) of the product. ^1H NMR (300MHz, CDCl_3): 2.70 (m, 3H), 2.93 (m, 1H), 4.62 (t, 9Hz, 1H), 6.95 (m, 3H), 7.86 (br s, 1H). FAB-MS: calculated for $\text{C}_{10}\text{H}_9\text{FINO}$ 305; found 306 ($\text{M}+\text{H}$, 100%).

10

Step C: 3-Azido-7-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

101mg (0.33mmol) of 3-iodo-7-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Step B) was dissolved in 8.3mL of methylene chloride and 105mg (0.66mmol, 2eq) of tetramethylguanidinium azide was added. The mixture was stirred at room temperature for 16 hours then water was added and the layers allowed to separate. The organic layer was removed, washed with water and brine, then dried over magnesium sulfate, filtered and solvents removed under vacuum to afford 66mg (0.30mmol, 90%) of the product. ^1H NMR (200MHz, CDCl_3): 2.28 (m, 1H), 2.45 (m, 1H), 2.73 (m, 1H), 2.93 (m, 1H), 3.86 (dd, 8, 11Hz; 1H), 7.0 (m, 3H), 8.15 (br s, 1H). FAB-MS: calculated for $\text{C}_{10}\text{H}_9\text{FN}_4\text{O}$ 220; found 221 ($\text{M}+\text{H}$, 100%).

30

Step D: 3-Amino-7-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

3-Azido-7-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (3.36g, 15.3mmol) (Step C) dissolved in dry tetrahydrofuran was treated with 4.00g

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(15.3mmol, 1eq) of triphenylphosphine and the resulting solution stirred at room temperature under nitrogen for 2 hours. Water (0.48mL, 2eq) was added and the mixture stirred at room temperature for 16 hours. Solvents were removed under vacuum and the residue purified by preparative HPLC on silica, eluting with methylene chloride/methanol (9:1) to afford 2.39g (12.3mmol, 81%) of product. ^1H NMR (200MHz, CD_3OD): 1.87 (m, 1H), 2.41 (m, 1H), 2.6-2.9 (m, 2H), 3.30 (dd; 8, 12Hz; 1H), 7.0 (m, 3H). FAB-MS: calculated for $\text{C}_{10}\text{H}_{11}\text{FN}_2\text{O}$ 194; found 195 ($\text{M}+\text{H}$, 100%).

15 Step E: 3-t-Butoxycarbonylamino-3-methylbutanoic acid
A solution of 4.65g (17.5mmol) of methyl 3-benzyloxycarbonylamino-3-methylbutanoate (Example 1, Step D) in 100mL absolute methanol at room temperature was treated with 3mL concentrated hydrochloric acid and hydrogenated at one atmosphere over 0.92g of 20% $\text{Pd}(\text{OH})_2/\text{C}$. After 16 hours, an additional 0.4g of catalyst was added and hydrogenation continued for 8 hours. The catalyst was removed by filtration through Celite and the filtrate concentrated under vacuum. The residue was redissolved in 50mL methylene chloride and treated with 6.0mL (5.7g, 26mol, 1.5eq) di-t-butyl-dicarbonate followed by 7.3mL triethylamine (5.3g, 52mmol, 3eq). The mixture was stirred at room temperature for 14 hours then diluted into 300mL of hexane/ethyl acetate (1:1) and washed with water (2x), saturated aqueous sodium bicarbonate and brine. The organic layer was removed, dried over

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magnesium sulfate, filtered and the solvents removed under vacuum. Purification by preparative HPLC on silica, eluting with hexane/ethyl acetate (6:1),
5 afforded 3.40g (14.7mmol, 84%) of the intermediate BOC-methyl ester as a colorless liquid.

This intermediate (3.40g, 14.7mmol) in 5mL methanol at room temperature was treated with 11mL of 2.0N NaOH (22mmol, 1.5eq) and the resulting mixture
10 stirred at room temperature for 24 hours. The mixture was diluted with 15mL water and washed with hexane. The aqueous layer was removed, cooled to 0°, and acidified by dropwise addition of saturated aqueous potassium hydrogen sulfate to a pH of 2-3.
15 The mixture was extracted with ethet (6x25mL); the combined extracts washed with brine, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue solidified upon standing to afford 3.11g (14.3mmol, 97%) of the product. ¹H NMR (200MHz, CDCl₃): 1.39 (s,6H), 1.44 (s,9H), 2.72 (s,2H). FAB-MS: calculated for C₁₀H₁₉NO₄ 217; found 218 (M+H, 54%).

Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[7-fluoro-
25 2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-
y1l-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Step E) and the amine obtained in Step D by the procedure described in Example 1, Step F. ¹H NMR (200MHz, CDCl₃): 1.33 (s,6H), 1.40 (s,9H), 1.90 (m,1H), 2.45 (d,15Hz,1H), 2.56 (d,15Hz,1H), 2.60 (m,1H), 2.73 (m,1H), 2.91 (m,1H), 4.50 (m,1H), 5.16 (br s,1H), 6.66 (d,7Hz,1H), 6.94

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(m,3H), 7.51 (br s,1H). FAB-MS: calculated for
 $C_{20}H_{28}FN_3O_4$ 393; found 394 ($M+H$, 42%).

5 Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[7-fluoro-
2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenyl-
methyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]-
methyl-1H-1-benzazepin-3-yl]butanamide

10 Prepared from the intermediate obtained in
Step F and N-triphenylmethyl-5-[2-(4'-bromomethyl-
biphen-4-yl)] tetrazole by the procedure described in
Example 1, Step K. 1H NMR (200MHz, $CDCl_3$): 1.34
(s,6H), 1.40 (s,9H), 1.74 (m,1H), 2.2-2.6 (m,3H),
2.43 (d,15Hz,1H), 2.53 (d,15Hz,1H), 4.43 (m,1H), 4.61
(d,14Hz,1H), 5.12 (d,14Hz,1H), 5.28 (br s,1H),
15 6.6-6.9 (m,3H), 6.9-7.5 (m,22H), 7.84 (m,1H).

20 Step H: 3-Amino-3-methyl-N-[7-fluoro-2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-
butanamide, trifluoroacetate

25 The intermediate obtained in Step G (360mg,
0.41mmol) was dissolved in 1mL of methanol and
treated dropwise with 1mL of 9N HCl. The mixture was
stirred at room temperature for 16 hours then all
volatiles were removed under vacuum and the residue
purified by reverse phase HPLC on C-18, eluting with
methanol/0.1% aqueous trifluoroacetic acid (linear
gradient; 60% methanol increased to 80% over 10
minutes) to afford 222mg (0.35mmol, 84%) of the title
compound. 1H NMR (300MHz, CD_3OD): 1.39 (s,3H), 1.42
(s,3H), 2.12 (m,1H), 2.3-2.7 (m,5H), 4.40
(dd,7,12Hz;1H), 4.85 (d,15Hz,1H), 5.30 (d,15Hz,1H),

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7.0-7.3 (m, 6H), 7.40 (m, 1H), 7.60 (m, 2H), 7.70 (m, 2H). FAB-MS: calculated for C₂₉H₃₀FN₇O₂ 527; found 528 (M+H, 100%).

5

EXAMPLE 32

10 3-Amino-3-methyl-N-[8-iodo-2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

Step A: 7-iodo-1-tetralone

15 4-(p-Iodophenyl)butyric acid (5.00g, 17.2mmol) was added to 48g of polyphosphoric acid and
the mixture heated at 95°-105°C for 1 hour, then
stirred at room temperature for 16 hours. The
reaction mixture was added to 500mL of ice/water and
extracted with ether (3x200mL). The combined
extracts were dried over magnesium sulfate and the
solvent removed under vacuum. The residue was
20 purified by medium pressure liquid chromatography on
silica, eluting with chloroform to yield 3.63g
(13.4mmol, 77%) of the product. ¹H NMR (200MHz,
CDCl₃): 2.11 (m, 2H), 2.62 (t, 5Hz, 2H), 2.90
25 (t, 5Hz, 2H), 6.99 (d, 8Hz, 1H), 7.74 (dd; 2, 8Hz; 1H), 8.30
(d, 2Hz, 1H). FAB-MS: calculated for C₁₀H₉I₂O 272;
found 273 (M+H, 100%).

30 Step B: 8-iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-iodo-1-tetralone by the
procedure described in Example 31, Step A. ¹H NMR
(200MHz, CDCl₃): 2.32 (m, 2H), 2.42 (m, 2H), 2.85

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(t, 6Hz, 2H), 7.05 (d, 8Hz, 1H), 7.44 (d, 2Hz, 1H), 7.56
(dd; 2, 8Hz; 1H). FAB-MS: calculated for $C_{10}H_{10}INO$
287; found 288 (M+H, 100%).

5

Step C: 3,8-diido-2,3,4,5-tetrahydro-1H-1-benzo-
zepin-2-one

10

Prepared from 8-iodo-2,3,4,5-tetrahydro-1H-1-
benzazepin-2-one by the procedure described in
Example 31, Step B. 1H NMR (200MHz, $CDCl_3$): 2.56
(m, 4H), 4.48 (t, 6Hz, 1H), 6.80 (d, 8Hz, 1H), 7.22
(d, 2Hz, 1H), 7.32 (dd; 2, 8Hz; 1H). FAB-MS: calculated
for $C_{10}H_9I_2NO$ 413; found 414 (M+H, 58%).

15

Step D: 3-Azido-8-iodo-2,3,4,5-tetrahydro-1H-1-benzo-
zepin-2-one

20

Prepared from 3,8-diido-2,3,4,5-tetrahydro-
1H-1-benzazepin-2-one by the procedure described in
Example 31, Step C. 1H NMR (200MHz, $CDCl_3$): 2.3-3.2
(m, 4H), 3.99 (m, 1H), 7.10 (d, 8Hz, 1H), 7.58 (m, 2H).
FAB-MS: calculated for $C_{10}H_9IN_4O$ 328; found 329
(M+H, 100%).

25

Step E: 3-Amino-8-iodo-2,3,4,5-tetrahydro-1H-1-benzo-
zepin-2-one

30

Prepared from 3-azido-8-iodo-2,3,4,5-tetra-
hydro-1H-1-benzazepin-2-one by the procedure
described in Example 31, Step D. 1H NMR (200MHz,
 $CDCl_3$): 1.92 (m, 1H), 2.56 (m, 2H), 2.82 (m, 1H), 3.40
(m, 1H), 6.98 (d, 8Hz, 1H), 7.32 (d, 2Hz, 1H), 7.45
(dd; 2, 8Hz; 1H), 7.60 (br s, 1H). FAB-MS: calculated
for $C_{10}H_{11}IN_2O$ 302; found 303 (M+H, 62%).

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Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[8-iodo-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

5 Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step E by the procedure described in Example 1, Step F. ^1H NMR (200MHz, CDCl_3): 1.33 (s,6H), 1.42 (s,9H), 1.80(m,1H), 2.24 (m,2H), 2.50 (m,3H), 4.45 (m,1H), 6.98 (d,8Hz,1H), 7.35 (d,2Hz,1H), 7.43 (dd;2,8Hz;1H). FAB-MS: calculated for $\text{C}_{20}\text{H}_{28}\text{IN}_3\text{O}_4$ 501; found 502 ($\text{M}+\text{H}$,20%).

10 15 Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[8-iodo-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]-methyl-1H-1-benzazepin-3-yl]-butanamide

20 Prepared from the intermediate obtained in Step F and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CD_3OD): 1.35 (s,6H), 1.42 (s,9H), 1.70 (m,1H), 2.22 (m,2H), 2.48 (m,3H), 4.40 (m,1H), 4.39 (d,14Hz,1H), 5.28 (d,14Hz,1H), 6.74 (m,2H), 6.8-7.6 (m,23H), 7.88 (m,1H).

25 30 Step H: 3-Amino-3-methyl-N-[8-iodo-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step G by the procedure described in Example 31, Step H. ^1H NMR (200MHz,

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CD₃OD): 1.32 (s, 3H), 1.37 (s, 3H), 2.04 (m, 1H),
2.1-2.6 (m, 3H), 2.50 (d, 4Hz, 2H), 4.30 (m, 1H), 4.76
5 (d, 14Hz, 1H), 5.24 (d, 14Hz, 1H), 6.96 (m, 3H), 7.15
(m, 2H), 7.60 (m, 6H). FAB-MS: calculated for
 $C_{29}H_{30}IN_7O_2$ 635; found 636 (M+H, 100%).

Example 33

10 3-Amino-3-methyl-N-[8-methoxy-2,3,4,5-tetrahydro-2-
oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]-
methyl]-1H-1-benzazepin-3-y1]-butanamide, trifluoro-
acetate

15 Step A: 8-Methoxy-2,3,4,5-tetrahydro-1H-1-benza-
zepin-2-one

Prepared from 7-methoxy-1-tetralone by the
procedure described in Example 31, Step A. ¹H NMR
(200MHz, CDCl₃): 2.19 (m, 2H), 2.32 (m, 2H), 2.70
20 (t, 6Hz, 2H), 3.76 (s, 3H), 6.57 (d, 2Hz, 1H), 6.66
(dd; 2, 8Hz; 1H), 7.09 (d, 8Hz, 1H). FAB-MS: calculated
for C₁₁H₁₃NO₂ 191; found 192 (M+H, 100%).

25 Step B: 3-Iodo-8-methoxy-2,3,4,5-tetrahydro-1H-1-
benzazepin-2-one

Prepared from 8-methoxy-2,3,4,5-tetrahydro-
1H-1-benzazepin-2-one by the procedure described in
Example 31, Step B. ¹H NMR (200MHz, CDCl₃): 2.6-3.1
(m, 4H), 3.88 (s, 3H), 4.76 (t, 6Hz, 1H), 6.68
30 (d, 2Hz, 1H), 6.81 (dd; 2, 8Hz; 1H), 7.20 (d, 2Hz, 1H).
FAB-MS: calculated for C₁₁H₁₂INO₂ 317; found 318
(M+H, 44%).

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Step C: 3-Azido-8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3-iodo-8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step C. ^1H NMR (200MHz, CDCl_3): 2.3-3.2 (m, 4H), 3.90 (s, 3H), 4.01 (m, 1H), 6.74 (d, 2Hz, 1H), 6.82 (dd; 2, 8Hz; 1H), 7.22 (d, 8Hz, 1H). FAB-MS: calculated for $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_2$ 232; found 233 ($\text{M}+\text{H}$, 100%).

Step D: 3-Amino-8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3-azido-8-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step D. ^1H NMR (200MHz, CDCl_3): 2.02 (m, 1H), 2.68 (m, 2H), 2.90 (m, 1H), 3.59 (m, 1H), 3.92 (s, 3H), 6.74 (d, 2Hz, 1H), 6.82 (dd; 2, 8Hz; 1H), 7.22 (d, 8Hz, 1H), 8.25 (br s, 1H). FAB-MS: calculated for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ 206; found 207 ($\text{M}+\text{H}$, 40%).

Step E: 3-t-Butoxycarbonylamino-3-methyl-N-[8-methoxy-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step D by the procedure described in Example 1, Step F. ^1H NMR (200MHz, CDCl_3): 1.44 (s, 6H), 1.50 (s, 9H), 1.80 (m, 1H), 2.80 (m, 5H), 3.86 (s, 3H), 4.62 (m, 1H), 6.62 (d, 2Hz, 1H), 6.76 (dd; 2, 8Hz; 1H), 7.20 (d, 8Hz, 1H). FAB-MS: calculated for $\text{C}_{21}\text{H}_{31}\text{N}_3\text{O}_5$ 405; found 406 ($\text{M}+\text{H}$, 42%).

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5 Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[8-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide

10 Prepared from the intermediate obtained in Step E and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CD₃OD): 1.47 (s, 6H), 1.55 (s, 9H), 1.80 (m, 1H), 2.42 (m, 2H), 2.60 (m, 3H), 3.84 (s, 3H), 4.62 (m, 1H), 4.78 (d, 14Hz, 1H), 5.30 (d, 14Hz, 1H), 6.79 (m, 2H), 7.08 (m, 12H), 7.42 (m, 11H), 7.98 (m, 1H).

15 Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[8-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-butanamide

20 Prepared from the intermediate obtained in Step F by the procedure described in Example 2, Step C. ^1H NMR (200MHz, CD₃OD): 1.42 (s, 6H), 1.50 (s, 9H), 2.10 (m, 1H), 2.56 (m, 5H), 3.82 (s, 3H), 4.43 (m, 1H), 4.92 (d, 15Hz, 1H), 5.31 (d, 15Hz, 1H), 6.86 (m, 1H), 6.97 (m, 2H), 7.0-7.3 (m, 4H), 7.64 (m, 3H), 8.05 (m, 1H). FAB-MS: calculated for C₃₅H₄₁N₇O₅ 639; found 640 (M+H, 20%).

25 Step H: 3-Amino-3-methyl-N-[8-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, mono(trifluoroacetate)

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The title compound was prepared from the intermediate obtained in Step G by the procedure described in Example 31, Step H. ^1H NMR (200MHz, CD₃OD): 1.43 (s,3H), 1.49 (s,3H), 2.15 (m,1H), 2.2-2.7 (m,5H), 3.85 (s,3H), 4.48 (m,1H), 5.04 (d,14Hz,1H), 5.28 (d,14Hz,1H), 6.92 (m,2H), 7.1-7.4 (m,4H), 7.65 (m,5H). FAB-MS: calculated for C₃₀H₃₃N₇O₃ 539; found 540 (M+H,100%).

10

Example 34

3-Amino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide,
15 hydrochloride

Step A: 3-(Trifluoromethyl)phenethyl tosylate

A solution of 10.0g (52.6mmol) of 3-(trifluoromethyl)phenethyl alcohol in 75mL of ether under nitrogen was treated with 10.53g (55.2mmol, 1.05eq) p-toluenesulfonyl chloride. The solution was cooled to 0° and treated with 7.67mL (5.57g, 55.0mmol, 1.05eq) of triethylamine. The mixture was stirred at 0° for 30 minutes then warmed to room temperature and stirred for 16 hours. The precipitate was removed by filtration and washed with ether. The combined filtrate and ether wash were evaporated under vacuum. The residue was redissolved in ethyl acetate and washed with 0.5N HCl and brine; the organic layer was removed, dried over sodium sulfate, filtered and concentrated under vacuum. Purification by flash chromatography on silica,

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eluting with 30% ethyl acetate/hexane, afforded
15.14g (44.0mmol, 84%) of the product. ^1H NMR
(200MHz, CDCl_3): 2.44 (s,3H), 3.03 (t,7Hz,2H), 4.26
(t,7Hz,2H), 7.2-7.5 (m,6H), 7.66 (d,8Hz,2H).
5 FAB-MS: calculated for $\text{C}_{16}\text{H}_{15}\text{F}_3\text{SO}_3$ 344; found 345
(M+H,8%).

10 Step B: 2-[2-(3-Trifluoromethylphenyl)-ethyl]propane-1,3-dioic acid, dimethyl ester
A suspension of 1.4g of 60% sodium hydride
oil dispersion (0.84g, 35mmol, 1.1eq) in 30mL of
tetrahydrofuran at room temperature under nitrogen
was treated dropwise over 15 minutes with a solution
15 of 4.0mL of dimethyl malonate (4.62g, 35mmol, 1.1eq)
in 30mL of tetrahydrofuran. After evolution of
hydrogen ceased, a solution of 11.03g (32.0mmol,
1.0eq) of 3-(trifluoromethyl)phenethyl tosylate (Step
A) in 30mL of tetrahydrofuran was added over 15
minutes. The mixture was heated at reflux for a
20 total of 21 hours. The mixture was filtered; the
filtrate was dried over magnesium sulfate, filtered
and concentrated under vacuum to afford 10.89g of
product which contained approximately 5% of unreacted
tosylate and was used without purification. ^1H NMR
25 (200MHz, CDCl_3): 2.24 (m,2H), 2.70 (t,8Hz,2H), 3.37
(t,8Hz,1H), 3.74 (s,6H), 7.3-7.5 (m,4H).

30 Step C: 4-(3-Trifluoromethylphenyl)-butanoic acid
The intermediate obtained in Step B (2.15g,
7.07mmol) was treated with 3.5mL of a 4.53M solution
of methanolic potassium hydroxide (15.9mmol, 2.2eq)
and the resulting mixture stirred at room temperature

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for 72 hours. The mixture was concentrated under vacuum and the solid residue redissolved in 4mL of concentrated hydrochloric acid and heated at reflux for 3 hours. The mixture was cooled, then extracted with methylene chloride (3x6mL); the combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was suspended in 20mL of water and treated with 700mg (8.3mmol) of sodium bicarbonate. The solution was washed with ether (2x20mL); the aqueous phase was removed and acidified (pH 1-2) with 2N HCl. The mixture was extracted with methylene chloride and the combined extracts dried over sodium sulfate, filtered and concentrated under vacuum. The residue was treated with 30mL of concentrated hydrochloric acid and the mixture heated at reflux for 20 hours. All volatiles were removed under vacuum to afford 1.12g (4.82mmol, 68%) of product.

¹H NMR (200MHz, CDCl₃): 1.98 (m, 2H), 2.40 (t, 8Hz, 2H), 2.74 (t, 8Hz, 2H), 7.3-7.5 (m, 4H).

Step D: 7-Trifluoromethyl-1-tetralone

Prepared from 4-(3-trifluoromethylphenyl)-butanoic acid by the procedure described in Example 32, Step A. ¹H NMR (200MHz, CDCl₃): 2.16 (m, 2H), 2.69 (t, 6Hz, 2H), 3.01 (t, 6Hz, 2H), 7.5 (m, 2H), 8.12 (d, 8Hz, 1H). EI-MS: calculated for C₁₁H₉F₃O 214; found 214 (M⁺, 40%).

30

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Step E: 7-Trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-trifluoromethyl-1-tetralone
by the procedure described in Example 31, Step A.
 ^1H NMR (200MHz, CDCl_3): 2.3 (m, 4H), 2.86 (t, 7Hz, 2H),
7.08 (d, 8Hz, 1H), 7.48 (m, 2H), 8.3 (br s, 1H).
FAB-MS: calculated for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{NO}$ 229; found 230
(M+H, 100%).

Step F: 3-Iodo-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step B. ^1H NMR (200MHz, CDCl_3): 2.8 (m, 4H), 4.68 (t, 8Hz, 1H), 7.11 (d, 8Hz, 1H), 7.52 (m, 2H), 7.95 (br s, 1H). FAB-MS: calculated for $\text{C}_{11}\text{H}_9\text{F}_3\text{INO}$ 355; found 356 (M+H, 100%).

Step G: 3-Azido-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3-iodo-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step C. ^1H NMR (200MHz, CDCl_3): 2.32 (m, 1H), 2.55 (m, 1H), 2.81 (m, 1H), 3.00 (m, 1H), 3.88 (dd; 8, 12Hz; 1H), 7.14 (d, 7Hz, 1H), 7.52 (m, 2H), 8.34 (br s, 1H). FAB-MS: calculated for $\text{C}_{11}\text{H}_9\text{F}_3\text{N}_4\text{O}$ 270; found 271 (M+H, 100%).

Step H: 3-Amino-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3-azido-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the

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procedure described in Example 31, Step D. ^1H NMR (200MHz, CD_3OD): 1.95 (m,1H), 2.46 (m,1H), 2.80 (m,2H), 3.35 (dd;8,12Hz;1H), 7.15 (d,8Hz,1H), 7.63 (m,2H). FAB-MS: calculated for $\text{C}_{11}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$ 244; found 245 ($\text{M}+\text{H}$,100%).

Step I: 3-t-Butoxycarbonylamino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step H by the procedure described in Example 1, Step F. ^1H NMR (200MHz, CDCl_3): 1.34 (s,6H), 1.42 (s,9H), 1.98 (m,1H), 2.50 (d,14Hz,1H), 2.63 (d,14Hz,1H), 2.7-3.0 (m,3H), 4.50 (m,1H), 6.75 (d,7Hz,1H), 7.10 (d,8Hz,1H), 7.51 (br s,2H), 7.94 (br s,1H). FAB-MS: calculated for $\text{C}_{21}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_4$ 443; found 444 ($\text{M}+\text{H}$,74%).

Step J: 3-t-Butoxycarbonylamino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in Step I and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CDCl_3): 1.36 (s,6H), 1.42 (s,9H), 1.71 (m,1H), 2.4-2.6 (m,5H), 4.44 (m,1H), 4.75 (d,15Hz,1H), 5.11 (d,15Hz,1H), 5.19 (br s,1H), 6.64 (d,7Hz,1H), 6.9-7.1 (m,10H), 7.2-7.5 (m,15H), 7.88 (m,1H).

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Step K: 3-amino-3-methyl-N-[7-trifluoromethyl-2,3,4,-
5 5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-
[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3-yl]butanamide, hydrochloride

The intermediate prepared in Step J (436mg, 0.47mmol) was dissolved in 4mL of methanol and treated dropwise with 4mL of 9N HCl. The mixture was stirred at room temperature for 16 hours then evaporated to dryness under vacuum. The dry solid was triturated with benzene (5x5mL) then with warm benzene (2x5mL) then dried to constant weight. Thus, 10 304mg (0.47mmol, 100%) of the title compound was obtained. ¹H NMR (200MHz, CD₃OD): 1.33 (s,3H), 1.36 (s,3H), 2.1-2.8 (m,6H), 4.30 (dd;8,12Hz;1H), 4.96 (d,15Hz,1H), 5.33 (d,15Hz,1H), 7.06 (d,8Hz,2H), 15 7.2-7.5 (m,3H), 7.5-7.7 (m,6H). FAB-MS: calculated for C₃₀H₃₀F₃N₇O₂ 577; found 578 (M+H,100%).

20 Example 35

3-amino-3-methyl-N-[8-chloro-2,3,4,5-tetrahydro-2-oxo-
1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3-yl]butanamide, trifluoroacetate

25 Step A: 7-Amino-1-tetralone
7-Nitrotetralone (2.5g, 13mmol) was suspended in 50mL of methanol and complete dissolution achieved by the addition of 10mL of tetrahydrofuran. The solution was hydrogenated at room temperature and 30 20-30psi over 100mg of 10% Pd/C for 2 hours. The mixture was filtered through Celite, washed with methanol and evaporated to dryness under vacuum to

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afford 2.1g (13mmol, 100%) of the product. ^1H NMR (300MHz, CDCl_3): 2.09 (m, 2H), 2.60 (t, 6Hz, 2H), 2.84 (t, 6Hz, 2H), 6.83 (m, 1H), 7.06 (d, 8Hz, 1H), 7.32 (d, 2Hz, 1H). FAB-MS: calculated for $\text{C}_{10}\text{H}_{11}\text{NO}$ 161; found 162 ($\text{M}+\text{H}$, 100%).

5 Step B: 7-chloro-1-tetralone

10 7-Amino-1-tetralone (500mg, 3.1mmol) was suspended in 3mL of water and treated with 3mL of concentrated hydrochloric acid with stirring. The mixture was cooled in an ice bath and treated dropwise with vigorous stirring with a solution of 241mg of sodium nitrite in 1.5mL of water (3.5mmol, 1.1eq). The mixture was stirred at 0-5° for 15 minutes then added dropwise to a cold solution of 366mg of CuCl (3.7mmol, 1.2eq) in 6mL of concentrated hydrochloric acid. The mixture was stirred for 5 minutes at 0° and 1 hour at room temperature. The 15 mixture was extracted with methylene chloride (3x15mL); the combined extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness under vacuum at room 20 temperature to give 550mg (3.05mmol, 98%) of the product. ^1H NMR (300MHz, CDCl_3): 2.16 (m, 2H), 2.67 (t, 6Hz, 2H), 2.95 (t, 6Hz, 2H), 7.22 (d, 8Hz, 1H), 7.44 (dd, 2,8Hz; 1H), 8.01 (d, 2Hz, 1H). FAB-MS: calculated for $\text{C}_{10}\text{H}_9\text{ClO}$ 180; found 181 ($\text{M}+\text{H}$, 10%).

25 30 Step C: 8-Chloro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 7-chloro-1-tetralone by the procedure described in Example 31, Step A. ^1H NMR

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(300MHz, CDCl₃): 2.23 (m, 2H), 2.37 (t, 6Hz, 2H), 2.80 (t, 6Hz, 2H), 7.1 (m, 3H), 9.08 (br s, 1H). FAB-MS: calculated for C₁₀H₁₀ClNO 195; found 195 (M⁺, 30%).

5

Step D: 3-Iodo-8-chloro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step C by the procedure described in Example 31, Step B. ¹H NMR (300MHz, CDCl₃): 2.72 (m, 3H), 2.90 (m, 1H), 4.67 (t, 8Hz, 1H), 7.05 (s, 1H), 7.18 (s, 2H), 7.71 (br s, 1H). FAB-MS: calculated for C₁₀H₉ClINO 320; found 321 (M+H, 100%).

15

Step E: 3-Azido-8-chloro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step D by the procedure described in Example 31, Step C. ¹H NMR (300MHz, DMF-d₇): 2.10 (m, 1H), 2.40 (m, 1H), 2.76 (m, 2H), 4.01 (dd; 8, 12Hz; 1H), 7.10 (d, 2Hz, 1H), 7.16 (dd; 2, 8Hz; 1H), 7.30 (d, 8Hz, 1H), 7.95 (br s, 1H). FAB-MS: calculated for C₁₀H₉ClN₄O 236; found 237 (M+H, 100%).

25

Step F: 3-Amino-8-chloro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step E by the procedure described in Example 31, Step D. ¹H NMR (300MHz, CDCl₃): 1.94 (m, 1H), 2.52 (m, 1H), 2.67 (m, 1H), 2.89 (m, 1H), 3.44 (m, 1H), 7.02 (d, 2Hz, 1H), 7.18 (m, 2), 7.70 (br s, 2H). FAB-MS: calculated for C₁₀H₁₁ClN₂O 210; found 211 (M+H, 84%).

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Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[8-chloro-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

5 Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step F by the procedure described in Example 1, Step F. ^1H NMR (300MHz, CDCl_3): 1.35 (s,6H), 1.42 (s,9H), 1.95 (m,1H), 2.4-2.8 (m,5H),
10 4.51 (m,1H), 5.22 (br s,1H), 6.73 (d,7Hz,1H), 7.02 (s,1H), 7.14 (br s,2H), 8.21 (br s,1H). FAB-MS:
calculated for $\text{C}_{20}\text{H}_{28}\text{ClN}_3\text{O}_4$ 409; found 410 (M+H,55%).

15 Step H: 3-t-Butoxycarbonylamino-3-methyl-N-[8-chloro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]-methyl-1H-1-benzazepin-3-yl]-butanamide

20 Prepared from the intermediate obtained in Step G and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K.

25 Step I: 3-Amino-3-methyl-N-[8-chloro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

30 Prepared from the intermediate obtained in Step H by the procedure described in Example 31, Step H. ^1H NMR (300MHz, CD_3OD): 1.40 (s,3H), 1.43 (s,3H), 2.12 (m,1H), 2.3-2.7 (m,5H), 4.30 (dd;8,12Hz;1H), 4.87 (d,15Hz,1H), 5.34 (d,15Hz,1H), 7.08 (d,8Hz,2H), 7.23 (d,8Hz,2H), 7.28 (s,2H), 7.45

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(s,1H), 7.59 (t,8Hz,2H), 7.70 (m,2H). FAB-MS:
calculated for C₂₉H₃₀ClN₇O₂ 543; found 544
(M+H, 43%).

5

Example 36

10 3-Amino-3-methyl-N-[8-fluoro-2,3,4,5-tetrahydro-2-oxo-
1-[[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-
1H-1-benzazepin-3-yl]butanamide, trifluoroacetate

Step A: 7-Fluoro-1-tetralone
In a specially designed Kel-F reactor
(cylindrical shape 1.25"od x 3" h equipped with a
15 screw cap and N₂ inlet-outlet) was placed hydrogen
fluoride-pyridine 6:4 solution (10mL, prepared by
diluting commercially available hydrogen
fluoride-pyridine 7:3 solution with dry pyridine).
7-amino-tetralone (644mg, 4.0mmol), (Example 35, Step
20 A) was added under N₂ and the solution was cooled to
0°. Sodium nitrite (304mg, 4.4mol, 1.1eq) was added
in portions and the mixture was stirred for 30
minutes. The mixture was then heated at 90°C for 1
hour with stirring. The reaction mixture was
25 quenched with approx. 60mL of ice/water and the solid
that separated extracted with methylene chloride
(3x30mL). The combined extracts were washed with
water and brine, dried over magnesium sulfate,
filtered and evaporated to dryness under vacuum at
room temperature. Purification by flash chromato-
30 graphy on silica, eluting with ethyl acetate/hexane
(5:95), afforded pure 7-fluoro-1-tetralone (367mg,
2.2mmol, 56%). ¹H NMR (300MHz, CDCl₃): 2.13 (m,2H),

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2.65 (t, 7Hz, 2H), 2.94 (t, 7Hz, 2H), 7.1-7.3 (m, 2H),
7.69 (dd; 2, 8Hz; 1H). EI-MS: calculated for C₁₀H₉FO
164; found 164 (M⁺, 71%).

5

Step B: 8-fluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one

Prepared from 7-fluoro-1-tetralone by the procedure described in Example 31, Step A. ¹H NMR (300MHz, CDCl₃): 2.22 (m, 2H), 2.38 (t, 6Hz, 2H), 2.78 (t, 6Hz, 2H), 6.75 (dd; 2, 8Hz; 1H), 6.84 (dt; 2, 8Hz; 1H), 7.16 (t, 8Hz, 1H), 8.35 (br s, 1H).

15

Step C: 3-Iodo-8-fluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one

Prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step B. ¹H NMR (300MHz, CDCl₃): 2.73 (m, 3H), 2.92 (m, 1H), 4.68 (t, 8Hz, 1H), 6.79 (dd; 2, 8Hz; 1H), 6.90 (dt; 2, 8Hz; 1H), 7.18 (t, 8Hz, 1H), 8.14 (br s, 1H).

20

Step D: 3-Azido-8-fluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one

Prepared from the intermediate obtained in Step C by the procedure described in Example 31, Step C. ¹H NMR (300MHz, CDCl₃): 2.30 (m, 1H), 2.51 (m, 1H), 2.74 (m, 1H), 2.93 (m, 1H), 3.88 (dd; 8, 12Hz; 1H), 6.80 (dd; 2, 8Hz; 1H), 6.89 (dt; 2, 8Hz; 1H), 7.21 (t, 8Hz, 1H), 8.10 (br s, 1H).

30

Step E: 3-Amino-8-fluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one

Prepared from the intermediate obtained in

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Step D by the procedure described in Example 31, Step D. ^1H NMR (300MHz, CDCl_3): 1.92 (m,1H), 2.52 (m,1H), 2.65 (m,1H), 2.86 (m,1H), 3.45 (m,1H), 6.78 (dd;2,8Hz;1H), 6.87 (dt;2,8Hz;1H), 7.20 (t,8Hz,1H), 8.56 (br s,1H). FAB-MS: calculated for $\text{C}_{10}\text{H}_{11}\text{FN}_2\text{O}^{+}$ 194; found 195 ($\text{M}+\text{H}, 100\%$).

Step E: 3-t-Butoxycarbonylamino-3-methyl-N-[8-fluoro-
2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-
y1l-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step E by the procedure described in Example 1, Step F. ^1H NMR (300MHz, CDCl_3): 1.35 (s,6H), 1.41 (s,9H), 1.93 (m,1H), 2.4-2.9 (m,5H), 4.54 (m,1H), 5.19 (br s,1H), 6.73 (m,2H), 6.88 (dt;2,8Hz;1H), 7.19 (dd;6,8Hz;1H), 8.07 (m,1H). FAB-MS: calculated for $\text{C}_{20}\text{H}_{28}\text{FN}_3\text{O}_4^{+}$ 393; found 394 ($\text{M}+\text{H}, 56\%$).

Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[8-fluoro-
2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenyl-
methyl)-tetrazol-5-y1][1,1'-biphenyl]-4-y1]-
methyl-1H-1-benzazepin-3-y1]-butanamide

Prepared from the intermediate obtained in Step F and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-y1)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (300MHz, CDCl_3): 1.36 (s,3H), 1.37 (s,3H), 1.42 (s,9H), 1.75 (m,1H), 2.3-2.6 (m,5H), 4.5 (m,2H), 5.25 (m,2H), 6.64 (d,7Hz,1H), 6.8-7.1 (m,11H), 7.2-7.5 (m,13H), 7.85 (m,1H).

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Step H: 3-Amino-3-methyl-N-[8-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-3-y1]-butanamide, trifluoroacetate

5

Prepared from the intermediate obtained in Step G by the procedure described in Example 31, Step H. ^1H NMR (300MHz, CD₃OD): 1.40 (s,3H), 1.43 (s,3H), 2.12 (m,1H), 2.3-2.7 (m,5H), 4.41 (dd;8,12Hz;1H), 4.88 (d,15Hz,1H), 5.34 (d,15Hz,1H), 7.0-7.2 (m,3H), 7.2-7.4 (m,5H), 7.5-7.8 (m,3H). FAB-MS: calculated for C₂₉H₃₀FN₇O₂ 527; found 528 (M+H,100%).

10

15

Example 37

3-Amino-3-methyl-N-[6-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-3-y1]-butanamide, trifluoroacetate

20

25

Step A: 4-(2-Fluorophenyl)butyric acid

Prepared from 4-(2-aminophenyl)butyric acid by the procedure described in Example 36, Step A. ^1H NMR (300MHz, CDCl₃): 1.95 (m,2H), 2.39 (t,7Hz,2H), 2.70 (t,7Hz,2H), 6.9-7.3 (m,4H). FAB-MS: calculated for C₁₀H₁₁FO₂ 182; found 182 (M⁺,75%).

30

Step B: 5-Fluoro-1-tetralone

Prepared from 4-(2-fluorophenyl)butyric acid by the procedure described in Example 32, Step A. ^1H NMR (300MHz, CDCl₃): 2.10 (m,2H), 2.60 (t,7Hz,2H), 2.88 (t,7Hz,2H), 7.1-7.3 (m,2H), 7.78 (d,8Hz,1H). EI-MS: calculated for C₁₀H₉FO 164; found 164 (M⁺,44%).

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Step C: 6-Fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 5-fluoro-1-tetralone by the procedure described in Example 31, Step A. ^1H NMR (300MHz, CDCl_3): 2.26 (m, 2H), 2.40 (t, 6Hz, 2H), 2.88 (t, 6Hz, 2H), 6.83 (d, 8Hz, 1H), 6.94 (t, 8Hz, 1H), 7.20 (m, 1H), 7.75 (br s, 1H). FAB-MS: calculated for $\text{C}_{10}\text{H}_{10}\text{FNO}$ 179; found 180 ($\text{M}+\text{H}$, 100%).

Step D: 3-Iodo-6-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step C by the procedure described in Example 31, Step B. ^1H NMR (300MHz, CDCl_3): 2.7-2.9 (m, 3H), 2.97 (m, 1H), 4.68 (t, 8Hz, 1H), 6.81 (d, 8Hz, 1H), 6.94 (t, 8Hz, 1H), 7.20 (m, 1H), 7.83 (br s, 1H).

Step E: 3-Azido-6-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step D by the procedure described in Example 31, Step C. ^1H NMR (200MHz, CDCl_3): 2.2-2.8 (m, 4H), 3.88 (dd; 8, 12Hz; 1H), 6.85 (d, 8Hz, 1H), 6.95 (t, 8Hz, 1H), 7.22 (m, 1H), 7.27 (br s, 1H).

Step F: 3-Amino-6-fluoro-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from the intermediate obtained in Step E by the procedure described in Example 31, Step D. ^1H NMR (300MHz, CD_3OD): 2.22 (m, 1H), 2.60 (m, 2H), 3.21 (m, 1H), 3.85 (dd; 8, 12Hz; 1H), 6.91 (d, 8Hz, 1H), 7.02 (t, 8Hz, 1H), 7.30 (m, 1H). FAB-MS:

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calculated for $C_{10}H_{11}FN_2O$ 194; found 195
(M+H, 100%).

5 Step G: 3-t-Butoxycarbonylamino-3-methyl-N-[6-fluoro-
2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-
yll-butanimide

Prepared from 3-t-butoxycarbonylamino-3-
methylbutanoic acid (Example 31, Step E) and the
10 amine obtained in Step F by the procedure described
in Example 1, Step F. 1H NMR (300MHz, $CDCl_3$): 1.36
(s, 6H), 1.43 (s, 9H), 1.91 (m, 1H), 2.4-2.8 (m, 3H),
3.18 (m, 2H), 4.54 (m, 1H), 5.18 (br s, 1H), 6.66
(d, 7Hz, 1H), 6.81 (d, 8Hz, 1H), 6.94 (t, 8Hz, 1H), 7.18
15 (m, 1H), 7.71 (br s, 1H). FAB-MS: calculated for
 $C_{20}H_{28}FN_3O_4$ 393; found 394 (M+H, 26%).

20 Step H: 3-t-Butoxycarbonylamino-3-methyl-N-[6-fluoro-
2,3,4,5-tetrahydro-2-oxo-1-[2'-(N-triphenyl-
methyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]-
methyl-1H-1-benzazepin-3-yll-butanimide

Prepared from the intermediate obtained in
Step G and N-triphenylmethyl-5-[2-(4'-bromomethyl-
biphen-4-yl)] tetrazole by the procedure described in
25 Example 1, Step K. 1H NMR (300MHz, $CDCl_3$): 1.38
(s, 6H), 1.45 (s, 9H), 1.81 (m, 1H), 2.18 (m, 1H),
2.4-2.7 (m, 3H), 2.89 (dd, 7, 14Hz; 1H), 4.52 (m, 1H),
4.77 (d, 15Hz, 1H), 5.09 (d, 15Hz, 1H), 5.29 (br s, 1H),
6.67 (d, 7Hz, 1H), 6.9-7.2 (m, 12H), 7.2-7.5 (m, 13H),
30 7.85 (m, 1H).

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Step I: 3-Amino-3-methyl-N-[6-fluoro-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

5

Prepared from the intermediate obtained in Step H by the procedure described in Example 31, Step H. ^1H NMR (300MHz, CD_3OD): 1.32 (s, 3H), 1.36 (s, 3H), 2.0-2.3 (m, 3H), 2.40 (br s, 2H), 3.00 (m, 1H), 4.35 (m, 1H), 4.87 (d, 15Hz, 1H), 5.20 (d, 15Hz, 1H), 7.00 (m, 3H), 7.1-7.4 (m, 4H), 7.5-7.7 (m, 4H). FAB-MS: calculated for $\text{C}_{29}\text{H}_{30}\text{FN}_7\text{O}_2$ 527; found 528 ($\text{M}+\text{H}, 100\%$).

15

EXAMPLE 38

3-Amino-3-methyl-N-[1,2,3,4,5,6-hexahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazocin-3-yl]-butanamide, trifluoroacetate

20

Step A: 3-benzyloxycarbonylamino-3-methyl-N-[1,2,3,-4,5,6-hexahydro-2-oxo-1H-1-benzazocin-3-yl]-butanamide

25

3-Azido-3,4,5,6-tetrahydro-1-benzazocin-2(1H)-one prepared by the method of Watthey, et al., J. Med. Chem., 28, 1511-1516 (1985) was reduced to 3-amino-3,4,5,6-tetrahydro-1-benzazocin-2(1H)-one by the procedure described in Example 1, Step A, then coupled with 3-benzyloxycarbonylamino-3-methylbutanoic acid (Example 1, Step E) by the procedure described in Example 1, Step F. ^1H NMR (200MHz, CDCl_3): 1.36 (s, 6H), 1.75 (m, 3H), 2.08 (m, 1H), 2.47 (m, 3H), 2.80(m, 1H), 4.13 (m, 1H), 5.12 (s, 2H), 5.79

30

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(s,1H), 6.86 (d,7Hz,1H), 7.0-7.4 (m,8H), 7.90
(s,1H). FAB-MS: calculated for C₂₄H₂₉N₃O₄ 423;
found 424 (M+H,100%).

5

Step B: 3-Benzylloxycarbonylamino-3-methyl-N-[1,2,3,-
4,5,6-hexahydro-2-oxo-1-[[2'-(N-triphenyl-
methyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]-
methyl-1H-1-benzazocin-3-yl]butanamide

10

Prepared from the intermediate obtained in
Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-
biphen-4-yl)] tetrazole by the procedure described in
Example 1, Step K. ¹H NMR (200MHz, CDCl₃): 1.42
(s,6H), 1.72 (m,4H), 2.42 (m,4H), 4.16 (m,1H), 4.49
15 (d,13Hz,1H), 5.10 (s,2H), 5.30 (d,13Hz,1H), 5.79
(s,1H), 6.80 (d,6Hz,2H), 6.9-7.6 (m,32H), 7.86 (m,1H).

15

20

Step C: 3-Amino-3-methyl-N-[1,2,3,4,5,6-hexahydro-2-
oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-
4-yl]methyl]-1H-1-benzazocin-3-yl]butan-
amide. trifluoroacetate

25

The title compound was prepared from the
intermediate obtained in Step B by the procedure
described in Example 1, Step L. ¹H NMR (200MHz,
CD₃OD): 1.28 (s,3H), 1.32 (s,3H), 1.44 (m,1H), 1.75
(m,3H), 2.05 (m,1H), 2.48 (m,3H), 4.00 (m,1H), 4.64
(d,13Hz,1H), 5.19 (d,13Hz,1H), 6.9-7.4 (m,8H),
7.4-7.7 (m,4H). FAB-MS: calculated for C₃₀H₃₃N₇O₂
523; found 524 (M+H,100%).

30

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Example 39

5 3-Amino-3-methyl-N-[1,2,3,4-tetrahydro-2-oxo-1-[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-
quinolin-3-y1]-butanamide, trifluoroacetate

10 Step A: 3-Benzylloxycarbonylamino-3-methyl-N-[1,2,3,4-tetrahydro-2-oxo-1H-1-quinolin-3-y1]-butanamide

15 Prepared as in Example 1, Step F from
3-amino-1,2,3,4-tetrahydroquinolin-2-one (prepared by
the method of Davis, et al; Arch. Biochem. Biophys.,
102, 48 (1963)) and 3-benzylloxycarbonylamino-3-
methylbutanoic acid (Example 1, Step E). ^1H NMR
(200MHz, CDCl_3): 1.42 (s, 6H), 2.68 (s, 2H), 2.86
(t, 13Hz, 1H), 3.00 (m, 1H), 4.67 (m, 1H), 5.00 (s, 2H),
6.9-7.3 (m, 9H). FAB-MS: calculated for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_4$
395; found 396 (M+1, 100%).

20 Step B: 3-Benzylloxycarbonylamino-3-methyl-N-[1,2,3,4-tetrahydro-2-oxo-1-[2'-(N-triphenylmethyl)-
tetrazol-5-y1][1,1'-biphenyl]-4-y1]methyl-1H-
1-quinolin-3-y1]-butanamide

25 Prepared from 3-benzylloxycarbonylamino-3-
methyl-N-[1,2,3,4-tetrahydro-2-oxo-1H-1-quinolin-3-
y1]-butanamide and N-triphenylmethyl-5-[2-(4'-bromo-
methylbiphen-4-y1)] tetrazole by the procedure
described in Example 1, Step K. ^1H NMR (200MHz,
 CD_3OD): 1.41 (s, 6H), 2.66 (s, 2H), 2.85 (t, 11Hz, 1H),
3.11 (m, 1H), 4.15 (m, 1H), 4.97 (d, 15Hz, 1H), 5.30
(d, 15Hz, 1H), 6.7-7.6, (m, 26H), 7.80 (m, 1H).

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Step C: 3-Amino-3-methyl-N-[1,2,3,4-tetrahydro-2-oxo-
1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
yl]methyl]-1H-1-quinolin-3-yl]-butanamide,
trifluoroacetate

5

The title compound was prepared from the
intermediate obtained in Step B by the procedure
described in Example 1, Step L. ^1H NMR (200MHz,
CD₃OD): 1.50 (s,3H), 1.52 (s,3H), 2.66 (m,2H), 3.16
10 (m,2H), 4.84 (m,1H), 5.17 (d,11Hz,1H), 5.39
(d,11Hz,1H), 7.0-7.4 (m,8H), 7.57 (m,4H). FAB-MS:
calculated for C₂₈H₂₉N₇O₂ 495; found 496
(M+H,100%).

15

Example 40

3-Benzylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

20

The title compound was prepared from
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(
1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-
benzazepin-3(R)-yl]-butanamide trifluoroacetate
(Example 1) and benzaldehyde by the procedure
described in Example 18. ^1H NMR (200MHz, CD₃OD):
1.42 (s,3H), 1.46 (s,3H), 2.0-2.6 (m,4H), 2.69 (br
s,2H), 4.12 (s,2H), 4.37 (dd;8,12Hz;1H), 4.90
(d,15Hz,1H), 5.18 (d,15Hz,1H), 6.97 (d,8Hz,2H),
7.1-7.7 (m,15H). FAB-MS: calculated for C₃₆H₃₇N₇O₂
30 599; found 600 (M+H,100%).

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Example 41

3-Isobutylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-
5 1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-
10 (1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-
benzazepin-3(R)-yl]-butanamide trifluoroacetate
(Example 1) and isobutyraldehyde by the procedure
described in Example 18. ^1H NMR (200MHz, CD₃OD):
0.99 (d, 8Hz, 3H), 1.00 (d, 8Hz, 3H), 1.35 (s, 3H), 1.39
15 (s, 3H), 1.8-2.6 (m, 7H), 2.81 (d, 7Hz, 2H), 4.32
(dd; 8, 12Hz; 1H), 4.92 (d, 15Hz, 1H), 5.14 (d, 15Hz, 1H),
7.00 (d, 8Hz, 2H), 7.1-7.4 (m, 6H), 7.5-7.7 (m, 4H).
FAB-MS: calculated for C₃₃H₃₉N₇O₂ 565; found 566
(M+H, 100%).

Example 42

20

3-Propylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
15 [[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-
25 (1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-
benzazepin-3(R)-yl]-butanamide trifluoroacetate
(Example 1) and propionaldehyde by the procedure
described in Example 18. ^1H NMR (200MHz, CD₃OD):
0.97 (t, 8Hz, 3H), 1.32 (s, 3H), 1.36 (s, 3H), 1.65
30 (m, 2H), 2.0-2.6 (m, 8H), 2.93 (t, 7Hz, 2H), 4.33
(dd; 7, 11Hz; 1H), 4.89 (d, 15Hz, 1H), 5.18 (d, 15Hz, 1H),

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6.99 (d, 8Hz, 2H), 7.10-7.35 (m, 6H), 7.45-7.65 (m, 4H).
FAB-MS: calculated for $C_{32}H_{37}N_7O_2$ 551; found 552
(M+H, 73%).

5

Example 43

10 3-(Cyclopropylmethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,
trifluoroacetate

15 The title compound was prepared from
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide trifluoroacetate
(Example 1) and cyclopropanecarboxaldehyde by the
procedure described in Example 18. 1H NMR (200MHz,
CD₃OD): 0.37 (m, 2H), 0.65 (m, 2H), 1.00 (m, 1H), 1.34
(s, 3H), 1.36 (s, 3H), 2.0-2.6 (m, 6H), 2.88 (d, 7Hz, 2H),
20 4.33 (dd, 7, 11Hz, 1H), 4.89 (d, 15Hz, 1H), 5.18
(d, 15Hz, 1H), 7.01 (d, 8Hz, 2H), 7.15-7.35 (m, 6H),
7.45-7.70 (m, 4H). FAB-MS: calculated for
 $C_{33}H_{37}N_7O_2$ 563; found 564 (M+H, 100%).

25

Example 44

30 3-(Cyclohexylmethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,
trifluoroacetate

The title compound was prepared from
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-

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benzazepin-3(R)-yl]-butanamide trifluoroacetate (Example 1) and cyclohexanecarboxaldehyde by the procedure described in Example 18. ^1H NMR (200MHz, CD₃OD): 0.8-1.4 (m, 6H), 1.33 (s, 3H), 1.37 (s, 3H), 1.5-1.9 (m, 5H), 2.0-2.6 (m, 6H), 2.80 (d, 7Hz, 2H), 4.32 (dd; 8, 12Hz; 1H), 4.92 (d, 15Hz, 1H), 5.14 (d, 15Hz, 1H), 7.00 (d, 8Hz, 2H), 7.10-7.35 (m, 6H), 7.45-7.70 (m, 4H). FAB-MS: calculated for C₃₆H₄₃N₇O₂ 605; found 606 (M+H, 100%).

Example 45

15 3-(4-hydroxybenzyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-(4-benzyloxybenzyl)amino-3-methyl-N-[2,3,-
20 4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-
y1)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benz-
azepin-3(R)-yl]-butanamide, trifluoroacetate
Prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-bi-
25 phenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butan-
amide trifluoroacetate (Example 1) and 4-benzyloxy-
benzaldehyde by the procedure described in Example
18. ^1H NMR (200MHz, CD₃OD): 1.32 (s, 3H), 1.35
(s, 3H), 2.0-2.7 (m, 6H), 4.10 (s, 2H), 4.36
(dd; 8, 12Hz; 1H), 4.91 (d, 15Hz, 1H), 5.02 (s, 2H), 5.09
(d, 15Hz, 1H), 6.98 (d, 8Hz, 6H), 7.1-7.6 (m, 15H).
30 FAB-MS: calculated for C₄₃H₄₃N₇O₃ 705; found 706 (M+H, 100%).

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Step B: 3-(4-Hydroxybenzyl)amino-3-methyl-N-[2,3,4,-
5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-
[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3(R)-yl]butanamide, trifluoroacetate

The intermediate obtained in Step A (14.6mg,
0.018mmol) dissolved in 1.5mL of methanol was
hydrogenated at room temperature and one atmosphere
over 10mg of 10% Pd/C for 2 hours. The reaction
mixture was filtered through Celite and the filtrate
concentrated under vacuum. The residue was purified
by reverse phase HPLC on C-18 eluting with
methanol/0.1% aqueous trifluoroacetic acid (linear
gradient: 60% methanol increased to 75% methanol
over 10 minutes) to afford 8.1mg (0.011mmol, 62%) of
the title compound. ¹H NMR (200MHz, CD₃OD): 1.40
(s,3H), 1.44 (s,3H), 2.0-2.7 (m,6H), 4.08 (s,2H),
4.36 (m,1H), 4.87 (d,15Hz,1H), 5.20 (d,15Hz,1H), 6.78
(d,8Hz,2H), 6.96 (d,8Hz,2H), 7.1-7.7 (m,12H).
FAB-MS: calculated for C₃₆H₃₇N₇O₃ 615; found 616
(M+H, 46%).

Example 46

3-Amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2'-(1H-
tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzo-
thiazepin-3(S)-yl]butanamide, trifluoroacetate

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-di-
hydro-4-oxo-1,5-benzothiazepin-3(S)-yl]-
butanamide

Prepared from 3(S)-amino-3,4-dihydro-1,5-
benzothiazepin-4(5H)-one (prepared from D-cysteine)

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(S-cysteine) by the method of Slade, et al, J. Med. Chem., 28, 1517-1521 (1985)) and 3-t-butoxycarbonyl-amino-3-methylbutanoic acid (Example 31, Step E) by the procedure described in Example 1, Step F. ^1H NMR (200MHz, CDCl_3): 1.38 (s,6H), 1.45 (s,9H), 2.32 (d,10Hz,1H), 2.50 (d,14Hz,1H), 2.70 (d,14Hz,1H), 2.92 (t,11Hz,1H), 3.93 (dd;7,11Hz;1H), 4.76 (m,1H), 7.02 (d,8Hz,1H), 7.1-7.3 (m,2H), 7.40 (t,8Hz,1H), 7.66 (d,7Hz,1H), 8.23 (br s,1H). FAB-MS: calculated for $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_4\text{S}$ 393; found 394 ($\text{M}+\text{H}$,36%).

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CD_3OD): 1.32 (s,6H), 1.39 (s,9H), 2.26 (d,7Hz,1H), 2.47 (d,14Hz,1H), 2.63 (d,14Hz,1H), 3.01 (t,11Hz,1H), 3.60 (dd;7,11Hz;1H), 4.76 (dd;7,11Hz;1H), 5.05 (br s,2H), 6.9-7.6 (m,26H), 7.80 (m,1H). FAB-MS (Li^+ spike): calculated for $\text{C}_{52}\text{H}_{51}\text{N}_7\text{O}_4\text{S}$ 870; found 876 ($\text{M}+\text{Li}$,100%).

Step C: 3-Amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure

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described in Example 31, Step H. ^1H NMR (200MHz, CD₃OD): 1.38 (s,3H), 1.40 (s,3H), 2.55 (br s,2H), 3.09 (t,11Hz,1H), 3.64 (dd;7,11Hz;1H), 4.65 (dd;7,11Hz;1H), 5.07 (d,15Hz,1H), 5.24 (d,15Hz,1H), 7.06 (d,8Hz,2H), 7.3-7.7 (m,10H). FAB-MS: calculated for C₂₈H₂₉N₇O₂S 527; found 528 (M+H,100%).

10

Example 47

3-Amino-3-methyl-N-[3,4-dihydro-1,1,4-trioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate

15

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,1,4-trioxo-1,5-benzothiazepin-3(S)-yl]-butanamide

20

To a solution of 88mg (0.22mmol) of

3-t-butoxycarbonylamino-3-methyl-N-[3,4-dihydro-4-oxo-1,5-benzothiazepin-3(S)-yl]-butanamide (Example 46, Step A) in 2mL of dry methylene chloride under nitrogen was added 38mg of solid sodium bicarbonate (0.44mmol, 2eq) followed by 106mg of 80% m-chloroperbenzoic acid (85mg mCPBA, 0.49mmol, 2.2eq).

25

for 3 hours then concentrated under vacuum. The residue was chromatographed on silica, eluting with ethyl acetate/hexane (7:3). The chromatographed material was redissolved in 50mL of ethyl acetate,

washed with 1:1 saturated aqueous sodium chloride/saturated aqueous potassium carbonate, then brine, dried over magnesium sulfate, filtered and

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evaporated under vacuum to afford 86mg (0.20mmol,
91%) of the product. ^1H NMR (200MHz, CDCl_3): 1.36
(s,3H), 1.38 (s,3H), 1.45 (s,9H), 2.51 (d,13Hz,1H),
2.83 (d,13Hz,1H), 3.58 (dd;12,14Hz;1H), 4.33
(dd;8,14Hz;1H), 4.90 (m,2H), 7.30 (m,2H), 7.46
(t,8Hz,1H), 7.70 (t,8Hz,1H), 8.07 (d,8Hz,1H), 8.70
(br s,1H). FAB-MS: calculated for $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_6\text{S}$
425; found 426 ($\text{M}+\text{H}$,32%).

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-di-hydro-1,1,4-trioxo-5-[[2'-(N-triphenyl-methyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]-methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CDCl_3): 1.35 (s,3H), 1.37 (s,3H), 1.47 (s,9H), 2.45 (d,13Hz,1H), 2.81 (d,13Hz,1H), 3.40 (dd;11,14Hz,1H), 4.18 (m,3H), 4.80 (m,2H), 5.65 (d,15Hz,1H), 6.9-7.6 (m,25H), 7.95 (m,2H). FAB-MS (Li^+ spike): calculated for $\text{C}_{52}\text{H}_{51}\text{N}_7\text{O}_6\text{S}$ 902; found 909 ($\text{M}+\text{Li}$,100%).

Step C: 3-Amino-3-methyl-N-[3,4-dihydro-1,1,4-trioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate

Prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H. ^1H NMR (200MHz, CD_3OD): 1.32 (br s,6H), 2.51 (br s,2H), 3.64 (dd;12,14Hz,1H), 3.98 (dd;8,14;1H), 4.54

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(d,16Hz,1H), 4.78 (m,1H), 5.43 (d,16Hz,1H), 7.08
(d,8Hz,2H), 7.30 (m,3H), 7.5-7.8 (m,6H), 8.00
(d,8Hz,1H). FAB-MS: calculated for C₂₈H₂₉N₇O₄S
5 559; found 560 (M+H,100%).

Example 48

10 3-Amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate
[diastereomer A]

15 Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,4-dioxo-1,5-benzothiazepin-3(S)-yl]-butanamide, diastereomers A and B

20 A solution of 179mg (0.46mmol) of 3-t-butoxycarbonylamino-3-methyl-N-[3,4-dihydro-4-oxo-1,5-benzothiazepin-3(S)-yl]-butanamide (Example 46, Step A) in 4.5mL of methanol/water (5:1) was treated with 102mg (0.48mmol, 1.05eq) of sodium periodate and stirred at room temperature for 48 hours. The reaction mixture was filtered and the filtrate concentrated under vacuum. The residue was redissolved in chloroform, dried over potassium carbonate, filtered and concentrated under vacuum. Purification by flash chromatography on silica, eluting with ethyl acetate, afforded 47mg (0.12mmol, 25%) of the less polar, minor diastereomer A in addition to 105mg (0.26mmol, 56%) of the more polar, major diastereomer B.

30 ¹H NMR (diastereomer A; 200MHz, CDCl₃):
1.37 (s,3H), 1.38 (s,3H), 1.45 (s,9H), 2.51
(d,13Hz,1H), 2.79 (d,13Hz,1H), 3.80 (m,2H), 4.78

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(m,1H), 4.95 (br s,1H), 7.14 (m,2H), 7.59 (m,2H), 7.93 (m,1H), 8.18 (br s,1H). FAB-MS: calculated for C₁₉H₂₇N₃O₅S 409; found 410 (M+H,29%).

5

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]butanamide,
diastereomer A

10

Prepared from diastereomer A obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ¹H NMR (200MHz, CDCl₃): 1.35 (s,3H), 1.36 (s,3H), 1.44 (s,9H), 2.45 (d,13Hz,1H), 2.72 (d,13Hz,1H), 3.61 (m,2H), 4.63 (m,1H), 4.86 (m,2H), 6.9-7.6 (m,25H), 7.81 (m,1H), 7.90 (m,1H). FAB-MS (Li⁺ spike): calculated for C₅₂H₅₁N₇O₅S 886; found 893 (M+Li,95%).

20

Step C: 3-Amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]butanamide, trifluoroacetate, diastereomer A

25

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H. ¹H NMR (200MHz, CD₃OD): 1.32 (br s,6H), 2.51 (br s,2H), 3.32 (dd;8,11Hz;1H), 3.95 (t,11Hz,1H), 4.55 (dd;8,11Hz;1H), 4.85 (d,15Hz,1H), 5.22 (d,15Hz,1H), 7.01 (d,8Hz,2H), 7.17 (d,8Hz,2H), 7.4-7.8 (m,8H). FAB-MS: calculated for C₂₈H₂₉N₇O₃S 543; found 544 (M+H,100%).

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Example 49

5 3-Amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, trifluoroacetate
[diastereomer B]

10 Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,4-dioxo-1,5-benzothiazepin-3(S)-yl]-butanamide, diastereomer B

15 Prepared from 3-t-butoxycarbonylamino-3-methyl-N-[3,4-dihydro-4-oxo-1,5-benzothiazepin-3(S)-yl]-butanamide (Example 46, Step A) by the procedure described in Example 48, Step A. ^1H NMR (diastereomer B; 200MHz, CDCl_3): 1.37 (s,3H), 1.38 (s,3H), 1.44 (s,9H), 2.48 (d,14Hz,1H), 2.68 (d,14Hz,1H), 3.30 (dd;11,15Hz;1H), 4.14 (dd;8,15Hz;1H), 4.86 (m,1H), 7.1 (d,8Hz,1H), 7.25 (m,1H), 7.41 (m,1H), 7.55 (m,1H), 8.81 (br s,1H).
20 FAB-MS: calculated for $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_5\text{S}$ 409; found 410 ($\text{M}+\text{H}$, 38%).

25 Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide, diastereomer B

30 Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CDCl_3): 1.38 (s,6H), 1.45 (s,9H), 2.50 (d,14Hz,1H), 2.72

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(d,14Hz,1H), 3.10 (dd;10,15Hz;1H), 4.05 (m,2H), 4.85
(m,1H), 5.08 (br s,1H), 5.68 (d,15Hz,1H), 6.9-7.5
(m,26H), 7.92 (m,1H). FAB-MS (Li⁺ spike):
calculated for C₅₂H₅₁N₇O₅S 886; found 893
(M+Li,64%).

Step C: 3-Amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
10 methyl]-1,5-benzothiazepin-3(S)-yl]butan-
amide, trifluoroacetate, [diastereomer B]
The title compound was prepared from the
intermediate obtained in Step B by the procedure
described in Example 31, Step H. ¹H NMR (200MHz,
15 CD₃OD): 1.33 (br s,6H), 2.53 (br s,2H), 3.29
(dd;11,14Hz;1H), 3.89 (dd;7,14;1H), 4.48 (d,16Hz,1H),
4.82 (m,1H), 5.33 (d,16Hz,1H), 7.0-7.7 (m,12H).
FAB-MS: calculated for C₂₈H₂₉N₇O₃S 543; found 544
(M+H,100%).

20

Example 50

3-Amino-3-methyl-N-[3,4-dihydro-3-oxo-4-[[2'-(1H-
tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1,4-
25 benzothiazin-2-yl]butanamide, mono(trifluoroacetate)

Step A: 2-Amino-3,4-dihydro-3-oxo-2H-1,4-benzo-
thiazine

Anhydrous ammonia gas was bubbled for one
hour through a suspension of 500mg (2.5mmol) of
30 2-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine
(prepared by the method of Worley, et al; J. Org.
Chem., 40, 1731-1734 (1975)) in 5mL of methylene

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chloride. The mixture was filtered through Celite and the filtrate evaporated under vacuum. The residue was triturated with 20mL of chloroform, 5 filtered and the filtrate evaporated under vacuum. Purification by flash chromatography on silica, eluting with ethyl acetate, afforded 185mg (1.0mmol, 41%) of the product. ^1H NMR (200MHz, CDCl_3): 2.00 (br s, 2H), 4.68 (br s, 1H), 6.9-7.4 (m, 4H), 9.05 (br s, 1H). FAB-MS: calculated for $\text{C}_8\text{H}_8\text{N}_2\text{OS}$ 180; found 181 ($\text{M}+\text{H}$, 54%).

10 Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl]-butanamide

15 Prepared from 2-amino-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (Step A) and 3-t-butoxycarbonyl-amino-3-methylbutanoic acid (Example 31, Step E) by the procedure described in Example 1, Step F.

20 ^1H NMR (200MHz, CD_3OD): 1.26 (s, 6H), 1.36 (s, 9H), 2.47 (d, 13Hz, 1H), 2.57 (d, 13Hz, 1H), 5.52 (br s, 1H), 6.31 (br s, 1H), 7.00 (m, 2H), 7.22 (m, 2H). FAB-MS: calculated for $\text{C}_{18}\text{H}_{25}\text{N}_3\text{O}_4\text{S}$ 379; found 380 ($\text{M}+\text{H}$, 26%).

25 Step C: 3-t-Butoxycarbonylamino-3-methyl-N-[3,4-dihydro-3-oxo-4-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-2H-1,4-benzothiazin-2-yl]-butanamide

30 Prepared from the intermediate obtained in Step B and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CDCl_3): 1.40

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(s, 6H), 1.42 (s, 9H), 2.53 (d, 14Hz, 1H), 2.92
5 (d, 14Hz, 1H), 4.86 (d, 16Hz, 1H), 4.92 (d, 8Hz, 1H), 5.29
(d, 16Hz, 1H), 5.49 (d, 8Hz, 1H), 6.85-7.50 (m, 26H), 7.92
(m, 1H).

Step D: 3-Amino-3-methyl-N-[3,4-dihydro-3-oxo-4-[[2'-
10 (1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-2H-1,4-benzothiazin-2-yl]-butanamide,
trifluoroacetate
The title compound was prepared from the
intermediate obtained in Step C by the procedure
described in Example 31, Step H. ^1H NMR (200MHz,
CD₃OD): 1.40 (s, 6H), 2.62 (s, 2H), 5.34 (s, 2H), 5.73
15 (s, 1H), 7.0-7.7 (m, 12H). FAB-MS: calculated for
C₂₇H₂₇N₇O₂S 513; found 514 (M+H, 100%).

Example 51

20 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[2-
phenylethyl]-1H-1-benzazepin-3-yl]-butanamide,
trifluoroacetate

Step A 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-
25 tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butan-
amide

Prepared from 3-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step A) and 3-benzyl-
oxycarbonylamino-3-methylbutanoic acid (Example 1,
Step E) by the procedure described in Example 1, Step
30 F. ^1H NMR (200MHz, CDCl₃): 1.38 (s, 3H), 1.39
(s, 3H), 1.82 (m, 1H), 2.52 (s, 2H), 2.5-3.0 (m, 3H),
4.51 (m, 1H), 5.07 (br s, 2H), 5.58 (br s, 1H), 6.68

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(d, 7Hz, 1H), 6.96 (d, 8Hz, 1H), 7.1-7.4 (m, 8H), 7.62 (br s, 1H). FAB-MS: calculated for C₂₃H₂₇N₃O₄ 409; found 410 (M+H, 100%).

5

Step B 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[2-phenylethyl]-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in
10 Step A and 2-phenethyl bromide by the procedure described in Example 3, Step A. ¹H NMR (200MHz, CDCl₃): 1.37 (s, 6H), 1.68 (m, 2H), 2.50 (m, 4H), 2.7-3.0 (m, 2H), 3.70 (m, 1H), 4.48 (m, 2H), 5.05 (s, 2H), 5.66 (s, 1H), 6.99 (m, 1H), 7.0-7.4 (m, 14H).
15 FAB-MS: calculated for C₃₁H₃₅N₃O₄ 513; found 514 (M+H, 100%).

20 Step C 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[2-phenylethyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 3, Step B. ¹H NMR (200MHz, CD₃OD): 1.34 (s, 3H), 1.42 (s, 3H), 2.0-2.4 (m, 1H), 2.58 (m, 3H), 2.85 (m, 2H), 3.90 (m, 1H), 4.58 (m, 1H), 4.90 (d, 15Hz, 1H), 5.0 (m, 1H), 5.15 (d, 15Hz, 1H), 7.0-7.5 (m, 9H). FAB-MS: calculated for C₂₃H₂₉N₃O₂ 379; found 380 (M+1, 100%).

30

Example 52

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[3-phenylpropyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

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Step A 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,-
5-tetrahydro-2-oxo-1-[3-phenylpropyl]-1H-1-
benzazepin-3-yl]-butanamide

5 Prepared from 3-benzylloxycarbonylamino-3-
methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-
y1]-butanamide (Example 51, Step A) and 3-phenylpropyl
bromide by the procedure described in Example 3, Step
A. ^1H NMR (200MHz, CDCl_3): 1.38 (s,6H), 1.82
10 (m,4H), 2.4-2.9 (m,7H), 3.45 (m,1H), 4.36 (m,1H),
5.02 (s,2H), 5.64 (s,1H), 6.69 (d,8Hz,1H), 6.9-7.4
(m,14H). FAB-MS: calculated for $\text{C}_{32}\text{H}_{37}\text{N}_3\text{O}_4$ 527;
found 528 ($\text{M}+\text{H}$,100%).

15 Step B 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-
1-[3-phenylpropyl]-1H-1-benzazepin-3-yl]-
butanamide, trifluoroacetate

20 The title compound was prepared from the
intermediate obtained in Step A by the procedure
described in Example 3, Step B. ^1H NMR (200MHz,
 CD_3OD): 1.21 (s,6H), 1.7-2.1 (m,2H), 2.1-2.4 (m,2H),
2.5-2.9 (m,6H), 3.46 (m,1H), 4.37 (m,2H), 6.9-7.3
(m,9H). FAB-MS: calculated for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_2$ 393;
found 394 ($\text{M}+1$,100%).

25 Example 53

30 4-Amino-4-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-
(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-
benzazepin-3-yl]-pentanamide, trifluoroacetate

Step A: 3-Amino-2,3,4,5-tetrahydro-1-[[2'-(1H-tetra-
zol-5-y1)[1,1'-biphenyl]-4-y1]methyl]-2H-1-
benzazepin-2-one, hydrochloride

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Prepared from 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step A) by the procedures described in Example 4, Steps A, B and C.

5 ^1H NMR (200MHz, CD_3OD): 2.17 (m,1H), 2.3-2.6 (m,3H), 3.80 (dd;8,12Hz;1H), 4.78 (d,15Hz,1H), 5.38 (d,15Hz,1H), 6.95 (d,8Hz,2H), 7.17 (d,8Hz,2H), 7.28 (m,2H), 7.38 (m,2H), 7.5-7.7 (m,4H). FAB-MS: calc. for $\text{C}_{24}\text{H}_{22}\text{N}_6\text{O}$ 410; found 411 ($\text{M}+\text{H}$,100%).

10 Step B: 4-Benzylloxycarbonylamino-4-methylpentanoic acid

Prepared from 2,2-dimethylglutaric acid by the procedures described in Example 1, Steps C, D and E. 15 ^1H NMR (200MHz, CDCl_3): 1.29 (s,6H), 2.02 (t,6Hz,2H), 2.34 (t,6Hz,2H), 5.06 (s,2H), 7.34 (s,5H), 10.5 (br s,1H).

20 Step C: 4-Benzylloxycarbonylamino-4-methyl-N-[2,3,4,-5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl-1H-benzazepin-3-yl]-pentanamide

25 Prepared from the intermediates obtained in Steps A and B by the procedure described in Example 4, Step D. 1 H NMR (200MHz, CD_3OD): 1.30 (s,6H), 1.9-2.6 (m,8H), 4.38 (m,1H), 4.86 (d,13Hz,1H), 4.98 (s,2H), 5.16 (d,13Hz,1H), 6.97 (d,8Hz,2H), 7.1-7.3 (m,11H), 7.4-7.7 (m,4H). FAB-MS: calculated for $\text{C}_{38}\text{H}_{39}\text{N}_7\text{O}_4$ 657; found 658 ($\text{M}+\text{H}$,20%).

30 Step D: 4-Amino-4-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-benzazepin-3-yl]-pentanamide, trifluoroacetate

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The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 1, Step H. ^1H NMR (200MHz, CD₃OD): 1.29 (s,3H), 1.31 (s,3H), 1.8-2.6 (m,8H), 4.29 (dd;8,12Hz;1H), 4.94 (d,13Hz,1H), 5.16 (d,13Hz,1H), 6.99 (d,8Hz,2H), 7.1-7.3 (m,6H), 7.4-7.7 (m,4H). FAB-MS: calculated for C₃₀H₃₃N₇O₂ 523; found 524 (M+H,100%)

10

Example 54

Piperidine-N'-(2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl)-4-carboxamide, trifluoroacetate

15

Step A: N-(t-Butoxycarbonyl)piperidine-4-carboxylic acid

To a suspension of 1.0g (7.74mmol) of piperidine-4-carboxylic acid in 20mL of methylene chloride at room temperature was added 1.13mL of triethylamine (0.82g, 8.1mmol, 1.05eq) followed by 1.87mL of di-t-butyl-dicarbonate (1.77g, 8.1mmol, 1.05eq). The mixture was stirred at room temperature for 48 hours then concentrated under vacuum. The residue was redissolved in ethyl acetate and the solution washed with 5% citric acid and brine, then dried over magnesium sulfate, filtered and evaporated under vacuum to afford 1.75g (7.63mmol, 98%) of the product. ^1H NMR (200MHz, CD₃OD): 1.42 (s,9H), 1.50 (m,2H), 1.84 (m,2H), 2.46 (m,1H), 2.86 (t,9Hz,2H), 3.91 (t,3Hz,1H), 3.98 (t,3Hz,1H). FAB-MS: calculated for C₁₁H₁₉NO₄ 229; found 230 (M+H,17%).

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Step B: N-(t-butoxycarbonyl)piperidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-piperidine-4-carboxamide

Prepared from N-(t-butoxycarbonyl)piperidine-4-carboxylic acid and 3-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one hydrochloride (Example 53, Step A) by the procedure described in Example 4, Step D.

^1H NMR (200MHz, CD₃OD): 1.42 (s, 9H), 1.4-2.9 (m, 11H), 4.05 (m, 3H), 4.30 (m, 1H), 4.81 (d, 15Hz, 1H), 5.22 (d, 15Hz, 1H), 6.98 (d, 8Hz, 2H), 7.1-7.3 (m, 6H), 7.4-7.7 (m, 4H). FAB-MS: calculated for C₃₅H₃₉N₇O₄ 621; found 622 (M+H, 7%).

Step C: Piperidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-4-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H. ^1H NMR (200MHz, CD₃OD): 1.7-2.7 (m, 8H), 3.00 (m, 3H), 3.38 (m, 2H), 4.31 (dd, 8, 12Hz; 1H), 4.86 (d, 15Hz, 1H), 5.20 (d, 15Hz, 1H), 6.99 (d, 8Hz, 2H), 7.1-7.4 (m, 6H), 7.4-7.7 (m, 4H). FAB-MS: calculated for C₃₀H₃₁N₇O₂ 521; found 522 (M+H, 100%).

30

Example 55

Piperidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-3-carboxamide, trifluoroacetate

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The title compound was prepared from piperidine-3-carboxylic acid and 3-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one hydrochloride (Example 53, Step A) by the procedures described in Example 54. ^1H NMR (200MHz, CD₃OD): 1.6-2.2 (m, 5H), 2.28 (m, 1H), 2.50 (m, 2H), 2.79 (m, 1H), 3.19 (m, 4H), 4.30 (m, 1H), 4.86 (d, 14Hz, 1H), 5.17 (d, 14Hz, 1H), 6.99 (m, 4H), 7.20 (m, 4H), 7.55 (m, 3H), 8.38 (m, 1H). FAB-MS: calculated for C₃₀H₃₁N₇O₂ 521; found 522 (M+H, 100%).

Example 56

Quinuclidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-3-carboxamide, trifluoroacetate

The title compound, as a mixture of four diastereomers, was prepared from racemic quinuclidine-3-carboxylic acid and 3-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one hydrochloride (Example 53, Step A) by the procedures described in Example 4, Step D. ^1H NMR (200MHz, CD₃OD): 1.7-2.7 (m, 8H), 3.0-3.7 (m, 8H), 4.32 (m, 1H), 4.8-5.2 (m, 2H), 7.00 (d, 8Hz, 2H) 7.1-7.4 (m, 6H), 7.4-7.7 (m, 4H). FAB-MS: calculated for C₃₂H₃₃N₇O₂ 547; found 531 (22%).

30

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Example 57

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
5 [[[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-
y1]-butanamide, trifluoroacetate

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[2,3,4,5-
10 tetrahydro-2-oxo-1H-1-benzazepin-3(R)-y1]-
butanamide

Prepared from 3-t-butoxycarbonylamino-3-
methylbutanoic acid (Example 31, Step E) and 3(R)-
amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one
(Example 1, Step B) by the procedure described in
15 Example 1, Step F. ^1H NMR (200MHz, CDCl_3): 1.37
(s,6H), 1.44 (s,9H), 1.95 (m,1H), 2.46 (d,15Hz,1H),
2.59 (d,15Hz,1H), 2.6-3.0, (m,3H), 4.53 (m,1H), 5.30
(br s,1H), 6.72 (d,7Hz,1H), 6.98 (d,8Hz,1H), 7.1-7.3
(m,3H), 7.82 (br s,1H). FAB-MS: calculated for
20 $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_4$ 375; found 376 ($\text{M}+\text{H}$, 70%).

Step B: 3-t-Butoxycarbonylamino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[[1,1'-biphenyl]-4-yl]-
25 methyl]-1H-1-benzazepin-3(R)-y1]-butanamide

Prepared from the intermediate obtained in
Step A and 4-chloromethylbiphenyl by the procedure
described in Example 1, Step K. FAB-MS: calculated
for $\text{C}_{33}\text{H}_{39}\text{N}_3\text{O}_4$ 541; found 542 ($\text{M}+\text{H}$, 31%).

30 Step C: 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-
oxo-1-[[[1,1'-biphenyl]-4-yl]methyl]-1H-1-
benzazepin-3(R)-y1]-butanamide, trifluoro-
acetate

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The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H. ^1H NMR (200MHz, CD₃OD): 1.33 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 4.38 (dd;8,12Hz,1H), 4.89 (d,15Hz,1H); 5.24 (d,15Hz,1H), 7.1-7.6 (m,13H). FAB-MS: calculated for C₂₈H₃₁N₃O₂ 441; found 442 (M+H,100%).

Example 58

10

3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carboxy][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

15

Step A: 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

20

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and 3-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step A) by the procedure described in Example 1, Step F. ^1H NMR (300MHz, CDCl_3): 1.34 (s, 6H), 1.41 (s, 9H), 1.90 (m, 1H), 2.45 (d, 15Hz, 1H), 2.56 (d, 15Hz, 1H), 2.65 (m, 1H), 2.76 (m, 1H), 2.92 (m, 1H), 4.53 (m, 1H), 5.20 (br s, 1H), 6.62 (d, 7Hz, 1H), 6.97 (d, 8Hz, 1H), 7.10-7.25 (m, 3H), 7.35 (br s, 1H). FAB-MS: calculated for $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_4$ 375; found 376 ($\text{M}+\text{H}$, 45%).

30

Step B: 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[(2'-t-butoxycarbonyl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

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Prepared from the intermediate obtained in Step A and t-butyl 4'-bromomethylbiphenyl-2-carboxylate (prepared by the method of D. J. Carini, et al, EP0 publication 324,377) by the procedure described in Example 1, Step K. ^1H NMR (300MHz, CDCl_3): 1.17 (s, 9H), 1.34 (s, 6H), 1.40 (s, 9H), 1.86 (m, 1H), 2.40-2.65 (m, 5H), 4.51 (m, 1H), 4.81 (d, 14Hz, 1H), 5.31 (s, 1H), 5.35 (d, 14Hz, 1H), 6.68 (d, 7Hz, 1H), 7.1-7.5 (m, 11H), 7.71 (m, 1H). FAB-MS: calculated for $\text{C}_{38}\text{H}_{47}\text{N}_3\text{O}_6$ 641; found 642 ($\text{M}+\text{H}$, 15%).

Step C: 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carboxy][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

The intermediate obtained in Step B (500mg, 0.78mmol) dissolved in 2mL of glacial acetic acid was treated with 2mL of 6N HCl and the mixture heated at 50°C for 3 hours. The mixture was concentrated under vacuum to a minimum volume, redissolved in 3mL of distilled water and lyophilized. The crusty solid was redissolved in 2mL of methanol and treated dropwise with stirring with 5mL of propylene oxide. The mixture was stirred at room temperature for 5 hours then filtered; the filter cake was washed with ether, air dried, then dried under vacuum to give 278mg (0.57mmol, 73%) of the title compound. ^1H NMR (300MHz, D_2O): 1.43 (s, 3H), 1.47 (s, 3H), 2.0-2.5 (m, 4H), 2.66 (m, 2H), 4.28 (dd; 7, 11Hz; 1H), 4.70 (d, 15Hz, 1H), 5.29 (d, 15Hz, 1H), 6.92 (m, 1H), 7.0-7.4 (m, 10H), 7.70 (m, 1H). FAB-MS: calculated for $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_4$ 485; found 486 ($\text{M}+\text{H}$, 100%).

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Example 59

5 3-Amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-
oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3-yl]-butanamide,
trifluoroacetate

10 Step A: 7-Methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

15 Prepared from 6-methoxy-1-tetralone by the
procedure described in Example 31, Step A. ^1H NMR
(200MHz, CDCl_3): 2.1-2.4 (m, 4H), 2.72 (t, 7Hz, 2H),
3.77 (s, 3H), 6.71 (d, 8Hz, 2H), 6.73 (s, 1H), 6.89
(d, 8Hz, 1H), 7.80 (br s, 1H). FAB-MS: calculated
for $\text{C}_{11}\text{H}_{13}\text{NO}_2$ 191; found 191 (M^+ , 60%).

20 Step B: 3-Iodo-7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

25 Prepared from 7-methoxy-2,3,4,5-tetrahydro-
1H-1-benzazepin-2-one by the procedure described in
Example 31, Step B. ^1H NMR (200MHz, CDCl_3):
2.5-3.0 (m, 4H), 3.89 (s, 3H), 4.64 (t, 8Hz, 1H), 6.75
(s, 1H), 6.77 (d, 8Hz, 1H), 6.94 (d, 8Hz, 1H), 7.70 (br s,
1H). FAB-MS: calculated for $\text{C}_{11}\text{H}_{12}\text{INO}_2$ 317;
found 317 (M^+ , 100%).

30 Step C: 3-Azido-7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

35 3-Iodo-7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (4.074g, 12.85mmol) and sodium azide
(4.178g, 64.3mmol, 5eq.) were dissolved in 50mL of

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dimethylformamide and heated with stirring at 60° for 2 hours. The solvent was evaporated under vacuum at room temperature and the residue redissolved in 150mL of ethyl acetate and washed with water (3x50mL) and brine (1x50mL). The organic layer was separated, dried over MgSO₄, filtered and evaporated to dryness under vacuum to yield 2.538g (10.94mmol, 85%) of product. ¹H NMR (200MHz, CDCl₃): 2.2-2.7 (m, 3H), 2.90 (m, 1H), 3.75 (s, 3H), 3.80 (m, 1H), 6.75 (m, 2H), 6.95 (d, 8Hz, 2H), 8.22 (br s, 1H). FAB-MS: calculated for C₁₁H₁₂N₄O₂ 232; found 233 (M+H, 30%).

Step D: 3-Amino-7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 3-azido-7-methoxy-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step D. ¹H NMR (200MHz, CDCl₃): 1.86 (m, 1H), 2.4-2.6 (m, 2H), 2.86 (m, 1H), 3.39 (m, 1H), 3.76 (s, 3H), 6.72 (d, 8Hz, 1H), 6.74 (s, 1H), 6.88 (d, 8Hz, 1H), 7.62 (br s, 1H). FAB-MS: calculated for C₁₁H₁₄N₂O₂ 206; found 208 (100%).

Step E: 3-t-Butoxycarbonylamino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step D by the procedure described in Example 1, Step F. ¹H NMR (200MHz, CDCl₃): 1.32 (s, 6H), 1.38 (s, 9H), 1.86 (m, 1H), 2.4-3.0 (m, 5H), 3.77 (s, 3H), 4.49 (m, 1H), 5.25 (br s, 1H), 6.68

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(d, 8Hz, 1H), 6.70 (s, 1H), 6.89 (d, 8Hz, 1H), 7.55 (br s, 1H). FAB-MS: calculated for $C_{21}H_{31}N_3O_5$ 405; found 428 ($M+Na$, 100%), 406 ($M+H$, 23%).

5

Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide

10

Prepared from the intermediate obtained in Step E and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step G. 1H NMR (200MHz, $CDCl_3$): 1.31 (s, 3H), 1.32 (s, 3H), 1.37 (s, 9H), 1.70 (m, 1H), 2.2-2.6 (m, 5H), 3.72 (s, 3H), 4.43 (m, 1H), 4.61 (d, 15Hz, 1H), 5.06 (d, 15Hz, 1H), 5.35 (br s, 1H), 6.62 (m, 3H), 6.9 (m, 10H), 7.25 (m, 12H), 7.83 (m, 1H).

20

Step G: 3-Amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, mono(trifluoroacetate)

25

The title compound was prepared from the intermediate obtained in Step F by the procedure described in Example 31, Step H. 1H NMR (200MHz, CD_3OD): 1.35 (s, 3H), 1.39 (s, 3H), 2.05 (m, 1H), 2.3-2.6 (m, 5H), 3.81 (s, 3H), 4.37 (dd; 7, 11Hz; 1H), 4.76 (d, 15Hz, 1H), 5.22 (d, 15Hz, 1H), 6.80 (d, 3Hz, 1H), 6.88 (dd; 3, 8Hz; 1H), 7.01 (d, 8Hz, 2H), 7.17 (d, 8Hz, 2H), 7.22 (d, 8Hz, 1H), 7.5-7.7 (m, 4H). FAB-MS: calculated for $C_{30}H_{33}N_7O_3$ 539; found 540 ($M+H$, 100%).

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Example 60

5 3-Amino-3-methyl-N-[7-hydroxy-2,3,4,5-tetrahydro-2-
oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3-yl]-butanamide,
trifluoroacetate

10 240mg (0.27mmol) of 3-t-butoxycarbonylamino-
3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-
15 (N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-
y1]methyl-1H-1-benzazepin-3-yl]-butanamide (Example
59, Step F) was dissolved in 4mL of methylene
chloride and the solution treated with 1.35mL of 1.0M
boron tribromide in methylene chloride (1.35mmol,
20 5eq.) and the mixture stirred at room temperature for
4 hours then quenched by the addition of 15mL of ice
water. The mixture was extracted with ethyl acetate
(2x20mL) and the combined organic phases were washed
with brine, dried over magnesium sulfate, filtered
and solvents removed in vacuo. The residue was
purified by reverse phase medium pressure liquid
chromatography on C8, eluting with methanol/0.1%
aqueous trifluoroacetic acid (55:45). In this
25 manner, 56mg (0.087mmol, 32%) of the title compound
was obtained as a colorless glass. ^1H NMR (200MHz,
CD₃OD): 1.39 (s,3H), 1.43 (s,3H), 2.07 (m,1H),
2.3-2.6 (m,5H), 4.42 (dd;5,8Hz;1H), 4.79 (d,11Hz,1H),
5.24 (d,11Hz,1H), 6.68 (d,2Hz,1H), 6.78
(dd;2,7Hz;1H), 7.06 (d,7Hz,2H), 7.18 (d,7Hz,1H), 7.21
30 (d,7Hz,2H), 7.5-7.7 (m,4H). FAB-MS: calculated for
C₂₉H₃₁N₇O₃ 525; found 526 (M+H,87%).

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Example 61

5 3-Amino-3-methyl-N-benzyl-N-[2,3,4,5-tetrahydro-2-
oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,
trifluoroacetate

10 Step A: 3(R)-(Benzylamino)-2,3,4,5-tetrahydro-1H-1-
benzazepin-2-one

15 A solution of 528mg (3.0mmol) of 3(R)-amino-
2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1,
Step B) in 45mL of absolute methanol at room
temperature was treated with 4.5g of powdered 3A
molecular sieves followed by dropwise addition of a
solution of 954mg (9.0mmol, 3eq.) of benzaldehyde in
15mL of methanol. The pH of the mixture was adjusted
to 7 by addition of trifluoroacetic acid then stirred
at room temperature for 2 hours. Sodium cyanoboro-
hydride (18mL of 1.0M THF solution; 18mmol, 6eq.) was
added and the mixture stirred at room temperature for
18 hours. The mixture was filtered and the filtrate
treated with 3mL of trifluoroacetic acid with stirring
for 3 hours, then all volatiles removed under vacuum
and the residue dissolved in 50mL of ethyl acetate.
The ethyl acetate solution was washed with water
(3x15mL), saturated aqueous sodium bicarbonate
(2x15mL) and 15mL of brine then dried over magnesium
sulfate, filtered and solvents removed under vacuum.
The residue was purified by chromatography on silica,
eluting with ethyl acetate/hexane (70:30), to afford
410mg (1.54mmol, 51%) of the product. ¹H NMR

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(200MHz, CDCl₃): 2.05 (m, 1H), 2.5-3.0 (m, 3H), 3.37 (dd; 7, 11Hz, 1H), 3.57 (d, 12Hz, 1H), 3.90 (d, 12Hz, 1H), 7.05 (d, 8Hz, 1H), 7.1-7.4 (m, 8H), 7.75 (br s, 1H).
5 FAB-MS: calculated for C₁₇H₁₈N₂O 266; found 267 (M+H, 75%).

10 Step B: 3-t-Butoxycarbonylamino-3-methyl-N-benzyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-(R)-y1l-butanimide]

15 A solution of 90mg (0.34mmol) of 3(R)-
(benzylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one in 1.5mL of tetrahydrofuran under nitrogen at room temperature was treated with 73mg (0.34mmol, 1.1eq.) of 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) followed by 94mg (0.38mmol, 1.1eq.) of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydro-quinoline (EEDQ). Most of the solvent was evaporated under a stream of nitrogen and the resulting reaction mixture (thick syrup approx. 0.3mL) was stirred for 3 days. The mixture was evaporated to dryness under vacuum and the residue purified by medium pressure liquid chromatography on silica, eluting with ethyl acetate/hexane (1:1) to afford 45mg (mmol, 33%) of product.
20 ¹H NMR (200MHz, CDCl₃): 1.28 (s, 3H), 1.32 (s, 3H), 1.35 (s, 9H), 2.16 (m, 2H), 2.35 (d, 14Hz, 1H), 2.58 (d, 14Hz, 1H), 2.60 (m, 1H), 2.81 (m, 1H), 4.70 (d, 18Hz, 1H), 4.99 (d, 18Hz, 1H), 5.37 (t, 10Hz, 1H), 5.83 (br s, 1H), 6.98 (d, 7Hz, 1H), 7.05-7.45 (m, 5H), 25 7.50-7.85 (m, 3H), 8.13 (t, 8Hz, 1H), 8.90 (m, 1H).
30 FAB-MS: calculated for C₂₇H₃₅N₃O₄ 465; found 466 (M+H, 48%).

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Step C: 3-Amino-3-methyl-N-benzyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

5 The title compound was prepared from the intermediate obtained in Step B and N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole by the methods described in Example 1, Step K and Example 31, Step H. ^1H NMR (400MHz, CD_3CN): 1.35 (s,3H),
10 1.36 (s,3H), 2.19 (m,1H), 2.38 (m,1H), 2.47
 (d,17Hz,1H), 2.7-2.9 (m,2H), 2.90 (d,17Hz,1H), 4.75
 (d,16Hz,1H), 4.93 (d,19Hz,1H), 5.03 (d,19Hz,1H), 5.22
 (dd;8,12Hz;1H), 5.48 (d,16Hz,1H), 7.2-7.5 (m,10H),
 7.6-7.8 (m,6H), 7.85 (br s,1H). FAB-MS: calculated
15 for $\text{C}_{36}\text{H}_{37}\text{N}_7\text{O}_2$ 599; found 600 ($\text{M}+\text{H}, 30\%$).

Example 62

20 3-Amino-3-methyl-N-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,
 trifluoroacetate

25 Step A: 3(R)-N-Methyl-N-benzylamino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

 A solution of 150mg (0.56mmol) of 3(R)-
 (benzylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 61, Step A) in 0.6mL of formic acid was treated with 0.047mL (0.56mmol, 1eq.) of 36% aqueous formaldehyde and the mixture heated at 80° with stirring for 24 hours. The mixture was cooled,

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treated with 0.8mL of 6N HCl, and all volatiles removed under vacuum. The residue was partitioned between 10mL of water and 10mL of methylene chloride; 1mL of 10% aqueous sodium carbonate was then added and the mixture shaken. The organic layer was separated and the aqueous layer extracted with an additional 20mL of methylene chloride. The combined extracts were dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on silica, eluting with 2.5% methanol in ethyl acetate, to give 98mg (0.35mmol, 63%) of product. ^1H NMR (200MHz, CDCl_3): 2.35 (s,3H), 2.35 (m,2H), 2.69 (m,1H), 2.88 (m,1H), 3.37 (dd;8,11Hz;1H), 3.80 (d,14Hz,1H), 3.90 (d,14Hz,1H), 6.90 (d,8Hz,1H), 7.05-7.35 (m,8H). FAB-MS: calculated for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}$ 280; found 281 ($\text{M}+\text{H}$,100%).

Step B: 3(R)-(Methylamino)-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A solution of 98mg (0.35mmol) of 3(R)-(N-methyl-N-benzyl)amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Step A) in 10mL of methanol was treated with one drop of concentrated sulfuric acid and the resulting solution hydrogenated at room temperature and 30-40psi over 20mg of 10% Pd/C for 20 hours. The mixture was filtered and the filtrate evaporated under vacuum. The residue was treated with 15mL of ethyl acetate, 4mL of water and 2mL of 10% aqueous sodium carbonate then shaken. The organic layer was separated, and the aqueous phase

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re-extracted with an additional 10mL of ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, filtered and the filtrate evaporated under vacuum to give 68mg (0.35mmol, 100%) of product. ^1H NMR (200MHz, CDCl_3): 1.85 (m, 1H), 2.30 (s, 3H), 2.35-2.65 (m, 2H), 2.73 (m, 1H), 3.10 (dd; 8, 12Hz; 1H), 6.97 (d, 8Hz, 1H), 7.1-7.3 (m, 3H), 7.5 (br s, 1H).

10 Step C: 3-t-Butoxycarbonylamino-3-methyl-N-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-(R)-y1]-butanamide

Prepared from 3-t-butoxycarbonylamino-3-methylbutanoic acid (Example 31, Step E) and the amine obtained in Step B by the procedure described in Example 1, Step F. ^1H NMR (200MHz, CDCl_3): 1.30 (br s, 15H), 2.19 (m, 1H), 2.42 (m, 1H), 2.5-2.8 (m, 3H), 2.91 (m, 1H), 3.15 (s, 3H), 5.32 (dd; 6, 8Hz; 1H), 5.52 (br s, 1H), 6.97 (d, 5Hz, 1H), 7.1-7.3 (m, 3H), 7.35 (br s, 1H).

25 Step D: 3-Amino-3-methyl-N-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, trifluoroacetate

Prepared from the intermediate obtained in Step C and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-y1)] tetrazole by the procedures described in Example 1, Step K and Example 31 Step H. ^1H NMR (200MHz, CD_3OD): 1.34 (s, 3H), 1.38 (s, 3H), 2.10 (m, 1H), 2.3-2.8 (m, 5H), 3.16 (s, 3H), 4.90 (d, 15Hz, 1H), 5.01

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(dd; 7, 11Hz; 1H), 5.13 (d, 15Hz, 1H), 7.02 (d, 8Hz, 2H),
7.19 (d, 8Hz, 2H), 7.2-7.4 (m, 4H), 7.5-7.7 (m, 4H).

FAB-MS: calculated for C₃₀H₃₃N₇O₂ 523; found 524
(M+H, 22%).

5

Example 63

10 2-Amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-
(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-
benzazepin-3(R)-yl]-propanamide, trifluoroacetate

15 Step A: 2-(t-Butoxycarbonylamino)-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-propanamide

15 Prepared from 2-(t-butoxycarbonylamino)-2-methylpropanoic acid and 3(R)-amino-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one (Example 1, Step B) by the procedure described in Example 1, Step F. ¹H NMR (200MHz, CDCl₃): 1.42 (s, 12H), 1.46 (s, 3H), 1.90 (m, 1H), 2.5-3.0 (m, 3H), 4.48 (m, 1H), 5.01 (br s, 1H), 6.97 (d, 8Hz, 1H), 7.1-7.3 (m, 3H), 7.9 (br s, 1H).
20 FAB-MS: calculated for C₁₉H₂₇N₃O₄ 361; found 362 (M+H, 30%).

25 Step B: 2-(t-Butoxycarbonylamino)-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-[N-(triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

30 Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-

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biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CDCl_3): 1.42 (s, 9H), 1.43 (s, 3H), 1.46 (s, 3H), 1.77 (m, 1H), 2.2-2.7 (m, 3H), 4.43 (m, 1H), 4.72 (d, 15Hz, 1H), 4.93 (br s, 1H), 5.09 (d, 15Hz, 1H), 6.9-7.5 (m, 26H), 7.86 (m, 1H).

Step C: 2-Amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, mono(trifluoroacetate)

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 31, Step H with final purification performed by reverse phase medium pressure liquid chromatography on C-8, eluting with methanol/0.1% aqueous trifluoroacetic acid (55:45). ^1H -NMR (200MHz, CD_3OD): 1.52 (s, 3H), 1.61 (s, 3H), 2.1-2.6 (m, 4H), 4.33 (dd; 8, 11Hz; 1H), 4.85 (d, 15Hz, 1H), 5.18 (d, 15Hz, 1H), 6.99 (d, 8Hz, 2H), 7.15 (d, 8Hz, 2H), 7.2-7.4 (m, 4H), 7.5-7.7 (m, 4H). FAB-MS: calculated for $\text{C}_{28}\text{H}_{29}\text{N}_7\text{O}_2$ 495; found 496 ($\text{M}+\text{H}$, 32%).

Example 64

Quinuclidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-3-carboxamide, trifluoroacetate

The title compound, as a mixture of two diastereomers, was prepared from racemic quinuclidine-3-carboxylic acid and 3(R)-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-

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2H-1-benzazepin-2-one hydrochloride (Example 4, Step C) by the procedure described in Example 4, Step D, with final purification by reverse phase medium pressure liquid chromatography on C-8, eluting with acetonitrile/0.1% aqueous trifluoroacetic acid (35:65). ^1H NMR (200MHz, CD_3OD): 1.7-2.6 (m, 8H), 3.00 (m, 1H), 3.1-3.3 (m, 6H), 3.65 (m, 1H), 4.32 (m, 1H), 4.8-5.2 (m, 2H), 7.00 (d, 8Hz, 2H), 7.1-7.3 (m, 6H), 7.5-7.7 (m, 4H). FAB-MS: calculated for $\text{C}_{32}\text{H}_{33}\text{N}_7\text{O}_2$ 547; found 548 ($\text{M}+\text{H}, 100\%$).

Example 65

15 3-Amino-2,2-dimethyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3(R)-yl]-propanamide, trifluoroacetate

Step A: 3-(Benzylloxycarbonylamino)-2,2-dimethyl-
propanoic acid

20 Prepared from 3-[benzylloxycarbonylamino]-
2,2-dimethylpropanoic acid, methyl ester (Example 1,
Step D) by the procedure described in Example 1, Step
E. ^1H NMR (200MHz, CDCl_3): 1.25 (s, 6H), 3.30
(d, 7Hz, 2H), 5.10 (s, 2H), 7.34 (s, 5H).

25 Step B: 3-(Benzylloxycarbonylamino)-2,2-dimethyl-N-
[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-
3(R)-yl]-propanamide

Prepared from 3-(benzylloxycarbonylamino)-2,2-
dimethylpropanoic acid and 3(R)-amino-2,3,4,5-tetra-
hydro-1H-[1]benzazepin-2-one (Example 1, Step B) by
the procedure described in Example 1, Step F. ^1H
NMR (200MHz, CDCl_3): 1.19 (s, 6H), 1.90 (m, 1H),

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2.6-3.0 (m,3H), 3.26 (d,6Hz,2H), 4.46 (m,1H), 5.07
(s,2H), 5.7 (br t,1H), 6.62 (d,7Hz,1H), 6.97
(d,8Hz,1H), 7.1-7.3 (m,3H), 7.3 (s,5H), 8.14 (br
s,1H). FAB-MS: calculated for C₂₃H₂₇N₃O₄ 409;
5 found 410 (M+H,100%).

Step C: 3-(t-Butoxycarbonylamino)-2,2-dimethyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yll-propanamide

10 A solution of 170mg (0.42mmol) of the intermediate obtained in Step B in 5mL of absolute methanol and one drop of trifluoroacetic acid was hydrogenated at room temperature and 1 atmosphere over 35mg of 20% palladium hydroxide on carbon for 4 hours. The mixture was filtered through Celite and solvent removed under vacuum to afford 165mg (0.42mmol, 100%) of the amine trifluoroacetate salt as a pale yellow solid.

15 The above intermediate was dissolved in 2mL of methylene chloride and treated with 108mg (0.49mmol, 1.2eq.) of di-t-butyl-dicarbonate followed by 0.12mL of triethylamine (87mg, 0.86mmol, 2eq.). After two hours at room temperature, the mixture was added to 20mL of ethyl acetate and washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate and brine. The organic layer was separated, dried over magnesium sulfate, filtered and solvents removed under vacuum. The residue was purified by medium pressure liquid chromatography on 20 silica, eluting with ethyl acetate/hexane (3:2) to afford 156mg (0.41mmol, 98%) of the product as a white solid. ¹H NMR (200MHz, CDCl₃): 1.18 (s,6H),

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1.39 (s,9H), 1.92 (m,1H), 2.6-3.0 (m,3H), 3.17
5 (d,6Hz,2H), 4.46 (m,1H), 5.25 (br s,1H), 6.69
(d,7Hz,1H), 6.98 (d,8Hz,1H), 7.1-7.3 (m,3H), 8.22 (br
(M+H,10%).

Step D: 3-(t-Butoxycarbonylamino)-2,2-dimethyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-(tri-

10 phenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-

4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-

propanamide

Prepared from the intermediate obtained in Step C and N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] tetrazole by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CDCl_3): 1.16 (s,3H), 1.17 (s,3H), 1.40 (s,9H), 1.74 (m,1H), 2.3-2.5 (m,3H), 3.16 (d,7Hz,2H), 4.40 (m,1H), 4.62 (d,15Hz,1H), 5.22 (d,15Hz,1H), 5.28 (br s,1H), 6.68 (d,7Hz,1H), 6.9-7.5 (m,26H), 7.85 (m,1H).

20

Step E: 3-Amino-2,2-dimethyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-propanamide, trifluoroacetate

25 The title compound was prepared from the intermediate obtained in Step D by the procedure described in Example 31, Step H with final purification performed by reverse phase medium pressure liquid chromatography on C-8, eluting with 30 methanol/0.1% aqueous trifluoroacetic acid (55:45). ^1H NMR (200MHz, CD_3OD): 1.24 (s,3H), 1.33 (s,3H), 2.1-2.6 (m,4H), 2.99 (br s,2H), 4.30 (dd;8,11Hz;1H),

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4.85 (d, 15Hz, 1H), 5.21 (d, 15Hz, 1H), 7.00 (d, 8Hz, 2H),
7.1-7.4 (m, 6H), 7.4-7.7 (m, 4H). FAB-MS: calculated
for $C_{29}H_{31}N_7O_2$ 509; found 510 ($M+H$, 100%).

5

Example 66

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[(2'-
(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-
benzazepin-3(S)-yl]butanamide, trifluoroacetate

10

Step A: 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(S)-yl]butanamide

Prepared from 3(S)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step B) and 3-benzylloxycarbonylamino-3-methylbutanoic acid (Example 1, Step E) by the procedure described in Example 1, Step F. FAB-MS: calculated for $C_{23}H_{27}N_3O_4$ 409; found 410 ($M+H$, 100%). $[a]_D = -160^\circ$ (c=1, $CHCl_3$).

25

Step B: 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[(2'-(N-triphenylmethyl)-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(S)-yl]butanamide

30

Prepared from the intermediate obtained in Step A and N-triphenylmethyl-5-(4'-bromomethylbiphen-2-yl)tetrazole by the procedure described in Example 1, Step K. 1H NMR (200MHz, $CDCl_3$): 1.38 (s, 3H), 1.40 (s, 3H), 1.67 (m, 1H), 2.2-2.5 (m, 5H), 4.44 (m, 1H),

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4.67 (d,14Hz,1H), 5.06 (s,2H), 5.12 (d,14Hz,1H), 5.63
(br s,1H), 6.64 (d,7Hz,1H), 6.9-7.5 (m,31H), 7.85
(m,1H).

5 Step C: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-
oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-
biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(S)-
y1]-butanamide, trifluoroacetate

10 The title compound was prepared from the
intermediate obtained in Step B by the procedure
described in Example 1, Step L. ¹H NMR
(200MHz,CD₃OD): 1.34 (s,3H), 1.38 (s,3H), 2.0-2.6
(m,6H), 4.34 (dd;7,11Hz;1H), 4.86 (d,15Hz,1H), 5.20
(d,15Hz,1H), 6.99 (d,8Hz,2H), 7.1-7.3 (m,6H),
15 7.45-7.70 (m,4H). FAB-MS: calculated for C₂₉H₃₁N₇O₂
509; found 510 (M+H,100%). [a]_D= -98° (c=.5,CH₃OH).

Example 67

20 3-(2-Fluoropropyl)amino-3-methyl-N-[2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-
4-y1]methyl]-1H-1-benzazepin-3(R)-y1]butanamide,
trifluoroacetate

25 To a cold (-78°C) solution of 3-(2-hydroxy-
propyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]methyl-
1H-1-benzazepin-3(R)-y1]butanamide (Example 22, 20mg,
0.029mmol) in 1.5mL of hydrogen fluoride-pyridine
under a nitrogen atmosphere, 0.2mL of DAST (diethyl-
aminosulfur trifluoride) was slowly added. The
reaction mixture was brought to room temperature and
stirred for 48 hours. Additional DAST (0.2mL) was
added at 24 hour intervals until no further reaction

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was detected by HPLC. The reaction mixture was repeatedly purified by reverse phase HPLC to afford 4mg of product. FAB-MS: calculated for C₃₂H₃₆N₇O₂F 569; found 570 (M+H, 100%). The product was converted into its hydrochloride salt by repeated evaporation of an aqueous 6N HCl/methanol solution. ¹⁹F NMR (CD₃OD): -75.4.

Example 68

10

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[(2-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

15

Step A: 3-Nitro-4-phenyltoluene

20

To a cold (0°C) solution of 4-methyl-2-nitroaniline (3.8g) in 11mL of HBF₄, an aqueous solution of sodium nitrite (1.7g in 3.4mL) was added dropwise. The reaction mixture was stirred for 10 minutes. The precipitate was collected and washed with cold aqueous HBF₄ (3mL), ethanol and ether to yield 1.72g of diazonium salt. The diazonium salt was suspended in benzene (76mL) and acetonitrile (7.6mL). Potassium acetate (1.53g) was added and the resulting mixture stirred under nitrogen in the dark at room temperature for 1.5 hr. The solid was removed by filtration and the filtrate washed with water (2x) and brine. The solution was dried with anhydrous sodium sulfate and then concentrated to afford 1.49g of crude product which could be chromatographed on silica gel (2:1 hexanes:CH₂Cl₂).

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Step B: 3-Amino-4-phenyltoluene

A solution of 2.4g of 3-nitro-4-phenyltoluene in 25mL of methanol was hydrogenated at room temperature and 40psi over 0.30g of 5% Pd/C catalyst.

5 The solution was filtered and the filtrate concentrated to give 1.98g of product. EI-MS: calculated for C₁₃H₁₃N: 183; found 183.

Step C: 3-Cyano-4-phenyltoluene

10 To a cold (0°C) suspension of 3-amino-4-phenyltoluene (1.97g) in 2.65mL of water and 2.65mL of 12N HCl was slowly added a solution of sodium nitrite (738mg) in 2mL of water. To this yellowish slurry, 10mL of fluoroboric acid was added with stirring. The cold mixture was filtered and the solid (2.02g) washed with cold fluoroboric acid, ethanol and ether. A solution of this diazonium salt (2.02g) in 5mL of DMSO was added dropwise with cooling to a mixture of CuCN and NaCN in DMSO (13.3mL). The reaction mixture was then diluted with water (20mL) and extracted repeatedly with benzene. The combined organic layers were washed with water (2x) and brine and then dried over anhydrous MgSO₄. Concentration under vacuum gave a reddish oil which was chromatographed on silica gel to give 0.788g of product.

Step D: N-Triphenylmethyl-5-[2'-(4'-methylbiphenyl-4-yl)]tetrazole

30 A solution of 3-cyano-4-phenyltoluene (390mg) and trimethyltin azide (525mg) in 2.5mL of toluene was heated at reflux for 24hr under

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nitrogen. The reaction mixture was concentrated and the residue suspended in 3.5mL of toluene. Tetrahydrofuran (0.25mL) was added followed by HCl gas until the solution became homogenous. The 5 mixture was concentrated and the residue (307mg) dissolved in 5mL of CH₂Cl₂ and treated with 504mg of triphenylmethyl chloride and 233mg of triethylamine under nitrogen. The mixture was stirred overnight and then diluted with CH₂Cl₂ and water. The layers 10 were separated and the aqueous layer further extracted with CH₂Cl₂. The combined organic layers were washed with water and brine, then dried over anhydrous magnesium sulfate. Concentration under vacuum afforded 935mg which was chromatographed on 15 silica gel eluting with hexanes:ethyl acetate (9:1) to give 615mg of product.

Step E: N-Triphenylmethyl-5-[2'-(4'-bromomethyl-biphenyl-4-yl)]tetrazole

20 A solution of N-triphenylmethyl-5-[2'-(methylbiphenyl-4-yl)]tetrazole (95.7mg), N-bromo-succinimide (35.5mg) and AIBN (2mg) in 4mL of CC₁₄ was heated at reflux for 4hr. The reaction mixture was filtered and the filtrate concentrated to give 25 129mg of product.

Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-benzazepin-3(R)-yl]butanamide

30 To a solution of 33.7mg of 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]butanamide (Example 57, Step

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A) in 0.5mL of dry dimethylformamide at room temperature was added 3.6mg of 60% sodium hydride oil dispersion under nitrogen. After 30 minutes, N-triphenylmethyl-5-[2'-(4'-bromomethylbiphenyl-4-yl)]-tetrazole (129mg) in 0.2mL of dry dimethyl-formamide was added and the resulting mixture stirred for 8hr at room temperature. The mixture was diluted with ethyl acetate and washed with water (2x) and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated unde vacuum. The crude product was chromatographed on silica gel eluting with ethyl acetate:hexanes (2:1) to give 16mg of pure product. FAB-MS: calculated for C₅₃H₅₃N₇O₂ 851; found 858 (M+Li).

15

Step G: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]butanamide

20

A solution of 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-benzazepin-3(R)-yl]butanamide (14mg) in 0.3mL of methanol and 0.3mL of 9N HCl was stirred overnight at room temperature and under nitrogen. The reaction mixture was diluted with benzene and freeze-dried to give 12mg of crude product which was purified by RP-HPLC on a Dynamax C18 column, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 60% methanol to 20% methanol in ten minutes) to give 9.0mg of the title compound. FAB-MS: calculated for C₂₉H₃₁N₇O₂ 510; found 511

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(M+1). ^1H NMR (400MHz, CD₃OD): 1.35 (s, 3H), 1.38 (s, 3H), 2.1-2.85 (m, 6H), 4.39 (dd; 8, 13Hz; 1H), 4.95 (d, 16Hz, 1H), 5.39 (d, 16Hz, 1H), 7.1 (m, 2H), 7.2-7.32 (m, 7H), 7.55-7.70 (m, 3H).

5

Example 69

10 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide, trifluoroacetate

Step A: 4-Methylphenyltrimethylstannane

15 41.4L of 1.0 M p-tolylmagnesium bromide in diethyl ether (41.4mol) was added dropwise, maintaining the temperature below -5°C, over 4 hours to a solution of 546g (2.79mol) of trimethyltin chloride in tetrahydrofuran (4L) under nitrogen at -10°C. The suspension was allowed to warm slowly to room temperature over 12h then saturated ammonium chloride solution (1L) was added followed by sufficient water (approximately 1L) to dissolve the precipitate. The solution was extracted with ether-hexane (1:1) (1x4L, 3x2L). The combined organic phases were washed with brine, dried over magnesium sulfate and the solvents removed under vacuum. Purification by flash chromatography on silica gel eluting with hexane/ethyl acetate (95:5) gave a pale yellow oil containing white crystals of 4,4'-dimethylbiphenyl which were removed by filtration to leave 711.3g (100%) of product. ^1H NMR (300MHz, CDCl₃): 0.30 (s, 9H), 2.34 (s, 3H), 7.19 (d, 7.7Hz, 2H), 7.40 (d, 7.7Hz, 2H).

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Step B: 4'-Methyl-1,1'-biphenyl-2-nitrile

A solution of 2.0g (10.98mmol) of 2-bromo-benzonitrile, 2.93g (11.54mmol) of 4-methylphenyl-trimethylstannane (Step A) and 0.385g (0.55mmol) of bis-triphenylphosphine palladium (II) chloride in 50mL of dry dimethylformamide under nitrogen was heated at 100°C for 5.5 hours. The reaction was cooled to room temperature. The reaction was poured into 150mL of water and extracted with ether (3x150mL). The combined ether extracts were washed with water (4x100mL) and brine (100mL), dried over magnesium sulfate, filtered and the solvents removed under vacuum. Purification by flash chromatography on silica gel, eluting with hexane/ether (85:15), afforded 1.69g (80%) of the product contaminated with about 10% of 2-methylbenzonitrile. ^1H NMR (200MHz, CDCl_3): 2.40 (s, 3H), 7.27 (d, 7Hz, 2H), 7.30-7.65 (m, 5H), 7.72 (d, 6Hz, 1H). FAB-MS: calculated for $\text{C}_{14}\text{H}_{11}\text{N}$ 193; found 193 (M^+ , 100%).

20

Step C: 4'-Bromomethyl-1,1'-biphenyl-2-nitrile

To a solution of 699mg (3.62mmol) of the intermediate obtained in Step B in 15mL of carbon tetrachloride under nitrogen was added 708.3mg (3.98mmol, 1.1 eq) of N-bromosuccinimide and 59mg (0.36mmol, 0.1eq) of azobisisobutyronitrile (AIBN). The resulting mixture was heated in the dark for 4 hours. The mixture was cooled to room temperature and filtered. The filtrate was concentrated under vacuum to afford 948mg (96%) of the product as a yellow solid. ^1H NMR (200MHz, CDCl_3): 4.51 (s, 2H),

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7.25-7.80 (m, 8H). FAB-MS: calculated for C₁₄H₁₀BrN 272; found 272, 274 (M⁺). ¹H NMR indicates the presence of minor amounts of starting material and dibromo derivative.

5

Step D: 3-[[1-[[2'-Cyano-[1,1'-biphenyl]-4-yl]-methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxopropylcarbamic acid, 1,1-dimethylethyl ester

10

To a solution of 0.83g (2.21mmol) of 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) in 6mL of dry dimethylformamide at room temperature under nitrogen was added 97mg of 60% sodium hydride dispersion in oil (58mg NaH, 2.43mmol, 1.1 eq). After stirring for 1 hour, a solution of 780mg (2.88mmol, 1.3 eq) of 4'-bromo-methyl-1,1'-biphenyl-2-nitrile (Step C) in 2.0mL of dimethylformamide was added via cannula. The flask which originally contained the bromide was washed with 1mL of dry dimethylformamide which was then added to the reaction mixture via cannula. After stirring at room temperature for 3 hours, the reaction was diluted with 200mL of ethyl acetate, washed with 50mL of water and 50mL of brine. The organic layer was separated, dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (6:4), to afford 1.13g (90%) of the product as a white foam. ¹H NMR (200MHz, CDCl₃):

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1.32 (s,3H), 1.40 (s,12H), 1.85 (m,1H), 2.35-2.70
(m,5H), 4.52 (m,1H), 4.90 (d,12Hz,1H), 5.21
(d,12Hz,1H), 6.70 (d,5Hz,1H), 7.10-7.65 (m,12H), 7.72
(d,6Hz,1H). FAB-MS: calculated for C₃₄H₃₈N₄O₄
5 566; found 567 (M+H).

Step E: 4'-[3(R)-[(3-t-Butoxycarbonylamino-3-methyl-

10 1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-

1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-

2-carboxamide

To a solution of 600mg (1.06mmol) of intermediate from Step D in 3.0mL of dimethylsulfoxide was added 15mg (0.106mmol) of anhydrous potassium carbonate followed by 0.88mL of 30% aqueous hydrogen peroxide. The resulting mixture was stirred at room temperature for 24 hours. The reaction was diluted with 100mL of chloroform and washed with water (30mL), 50% saturated aqueous sodium bisulfite (30mL) and brine (30mL). The organic layer was dried over sodium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate, to afford 551.4mg (90%) of the product as a white solid. ¹H NMR (200MHz,CDCl₃): 1.30 (s,3H), 1.37 (s,12H), 1.85 (m,1H), 2.45-2.70 (m,5H), 4.50 (m,1H), 4.85 (d,12Hz,1H), 5.18 (s,1H), 5.25 (d,12Hz,1H), 5.65 (s,1H), 6.78 (d,5Hz,1H), 7.2-7.5 (m,12H), 7.70 (dd;5,1Hz;1H). FAB-MS: calculated for C₃₄H₄₀N₄O₅ 584; found 586.

30

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Step F: 4'-[[(3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl)methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate]

5 To a slurry of 551mg (0.942mmol) of intermediate from Step E in 2mL of dry methylene chloride was added 5 drops of anisole followed by 2mL of trifluoroacetic acid. After stirring for 2 hours at room temperature all volatiles were removed under 10 vacuum. The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (55:45) to afford 535mg (95%) of the title compound as a white solid. ^1H NMR (200MHz, CD_3OD): 1.42 (s, 3H), 1.48 (s, 3H), 2.00-2.65 (m, 6H), 4.42 (dd; 7, 10Hz; 1H), 4.95 (d, 14Hz, 1H), 5.25 (d, 14Hz, 1H), 7.2-7.6 (m, 12H). FAB-MS: calculated for $\text{C}_{29}\text{H}_{32}\text{N}_4\text{O}_3$ 484; found 485 ($\text{M}+\text{H}$, 100%).

20

Example 70

4'-[[(2,3,4,5-Tetrahydro-3(R)-[[3-[(2(R)-hydroxy-propyl)amino]-3-methyl-1-oxobutyl]amino-2-oxo-1H-1-benzazepin-1-yl)methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate]

25 To a solution of 0.75g (1.25mmol) of 4'-[[(3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl)methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate (Example 69) in 15mL dry methanol was added 0.35mL (2.50mmol) of triethylamine, 4.0g of dry 4A powdered molecular sieves followed by a solution of 1.3g

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(7.5mmol) of 2(R)-benzyloxypropanal (prepared according to the procedure of Hanessian and Kloss, Tetrahedron Lett. 1985, 26, 1261-1264.) in 5mL of dry methanol. The pH of the mixture was carefully
5 adjusted to 6.5 with glacial acetic acid. The reaction was stirred for 5 hours at which time 7.5mL (7.5mmol) of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran was added by syringe. The reaction was stirred for 3 days then
10 filtered through a pad of Celite. To the filtrate was added 5.0mL of trifluoroacetic acid (CAUTION! evolution of hydrogen cyanide) and the resulting mixture stirred for three hours. The solvent was removed under vacuum to afford 5.0g of a clear oil.
15 The crude intermediate was dissolved in 30mL of methanol and placed in a shaker bottle. To the solution was added 1mL of trifluoroacetic acid followed by 1.2g of 30% palladium on carbon. The mixture was hydrogenated at room temperature and 40psi for 36 hours. The mixture was filtered through Celite and the solvent removed under vacuum. The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid
20 (60:40) to afford 640mg (78%) of the title compound as a white solid. ^1H NMR (200MHz, CD_3OD): 1.22 (d, 8Hz, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 2.12 (m, 2H), 2.32 (m, 2H), 2.62 (m, 4H), 2.80 (dd; 8, 11Hz; 1H), 3.08 (dd; 3, 11Hz; 1H), 3.92 (m, 1H), 4.39 (dd; 7, 12Hz; 1H),
25 5.02 (d, 14Hz, 1H), 5.18 (d, 14Hz, 1H), 7.20-7.55 (m, 12H). FAB-MS: calculated for $\text{C}_{32}\text{H}_{38}\text{N}_4\text{O}_4$ 542; found 544 ($\text{M}+\text{H}$, 100%).

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Example 71

5 4'-[[3(R)-[[3-[(2(S),3-Dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

To a solution of 0.585g (0.98mmol) of
10 4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate
(Example 69) in 15mL dry methanol was added 0.27mL
(1.95mmol) of triethylamine, 2.5g of dry 4A powdered
15 molecular sieves followed by a solution of 1.3g
(10mmol) of D-glyceraldehyde acetonide (used crude as
prepared according to the procedure of Hertel, L.W.;
Grossman, C. S.; Kroin, J.S. Synth. Comm. 1991, 21,
151-154.) in 5mL of dry methanol. The pH of the
mixture was carefully adjusted to 6.5 with glacial
acetic acid (7 drops). The reaction was stirred for
20 3 hours at which time 4.9mL (4.9mmol) of a 1.0M
solution of sodium cyanoborohydride in tetrahydro-
furan was added via syringe. The reaction was
stirred for 20 hours then filtered through a pad of
Celite. To the filtrate was added 5.0mL of
25 trifluoroacetic acid (CAUTION! hydrogen cyanide
evolved), 5.0ml of water and 5 drops of concentrated
hydrochloric acid. The resulting mixture was stirred
for 24 hours. The solvent was removed under vacuum
30 to afford a clear oil which was purified by reverse
phase medium pressure liquid chromatography on C-8
eluting with methanol/ 0.1% aqueous trifluoroacetic
acid (60:40) to afford 590mg (90%) of the title

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compound as a white solid. ^1H NMR (200MHz, CD₃OD): 1.35 (s, 3H), 1.39 (s, 3H), 2.12 (m, 1H), 2.31 (m, 1H), 2.60 (m, 4H), 2.98 (dd; 8, 12Hz; 1H), 3.19 (dd; 3, 12Hz; 1H), 3.55 (dd; 3, 6Hz; 2H), 3.83 (m, 1H), 4.40 (dd; 8, 11Hz; 1H), 5.02 (d, 15Hz, 1H), 5.15 (d, 15Hz, 1H), 7.20-7.55 (m, 12H). FAB-MS: calculated for C₃₂H₃₈N₄O₅ 558; found 560 (100%).

Example 72

10

N-Ethyl-4'--[[3(R)-[(3-amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

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Step A: 4'--[[2,3,4,5-Tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxy)carbonyl]amino]butyl]-amino]-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxylic acid
1,1-dimethylethyl ester

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To a solution of 1.22g (3.0mmol) of 3-benzyl-oxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 1, Step F) in 10mL of dry dimethylformamide under nitrogen was added 131.6mg (3.29mmol) of 60% sodium hydride in oil. After stirring for 20 minutes, a solution of 1.14g (3.29mmol) of t-butyl 4'-bromo-methyl-1,1'-biphenyl-2-carboxylate (prepared according to the procedure of D.J. Carini, et. al. EPO publication 324,377) in 2.5mL of dimethylformamide

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was added by cannula. The flask which originally contained the bromide was rinsed with 2.5mL dimethylformamide which was added to the reaction

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mixture. After stirring at room temperature for 2 hours, the reaction was diluted with 400mL of ethyl acetate, washed with 100mL of water and 100mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/hexane (55:45) to afford 1.74g (96%) of the product as a white foam. ^1H NMR (200MHz, CDCl_3): 1.15 (s, 9H), 1.45 (s, 3H), 1.48 (s, 3H), 1.76 (m, 1H), 2.35-2.62 (m, 5H), 4.48 (m, 1H), 4.79 (d, 14Hz, 1H), 5.04 (t, 12Hz, 2H), 5.35 (d, 14Hz, 1H), 6.70 (d, 6Hz, 1H), 7.10-7.45 (m, 17H), 7.72 (m, 1H). FAB-MS: calculated for $\text{C}_{41}\text{H}_{45}\text{N}_3\text{O}_6$ 675; found 683 (M+Li).

Step B: 4'-[[2,3,4,5-Tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxy)carbonyl]amino]buty1]-amino]-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxylic acid

To a solution of 150mg (0.22mmol) of the intermediate from Step A in 1mL of dry methylene chloride was added 2 drops of anisole followed by 1mL of trifluoroacetic acid. The solution was stirred for 4 hours at room temperature. The solvent was removed under vacuum and the resulting oil was azeotroped with carbon tetrachloride (3x20mL) to afford 140mg (100%) of product as a white foam. ^1H NMR (200MHz, CDCl_3): 1.38 (s, 6H), 1.65 (m, 1H), 2.10-2.40 (m, 3H), 2.61 (s, 2H), 4.45 (m, 1H), 4.62 (d, 14Hz, 1H), 5.06 (s, 2H), 5.27 (d, 14Hz, 1H), 7.00-7.36 (m, 15H), 7.42 (m, 1H), 7.55 (m, 1H), 7.68 (d, 7Hz, 1H), 7.95 (dd, 2,8Hz; 1H), 8.18 (br s, 1H). FAB-MS: calculated for $\text{C}_{37}\text{H}_{37}\text{N}_3\text{O}_6$ 619; found 642 (M+Na).

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Step C: N-Ethyl-4'--[[3(R)-[[3-(benzyloxycarbonyl)-amino-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl][1,1'-biphenyl-2-carboxamide]

To a slurry of 14mg (0.169mmol) of ethylamine hydrochloride in 1mL of dry methylene chloride under nitrogen at 0°C was added 0.047mL (0.339mmol) of triethylamine followed by a solution of 70mg (0.113mmol) of the intermediate from Step B in 1mL of methylene chloride. To this mixture was added 75mg (0.169mmol) of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. The reaction mixture was slowly warmed to room temperature. After 2 hours the reaction was diluted with 75mL of ethyl acetate, washed with 25mL of 5% aqueous citric acid, 25mL of saturated aqueous sodium bicarbonate and 25mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/hexane (9:1) to afford 74mg (100%) of the product as a white foam. ^1H NMR (200MHz, CDCl_3): 0.75 (t, 6Hz, 3H), 1.35 (s, 3H), 1.38 (s, 3H), 1.76 (m, 2H), 2.35-2.62 (m, 5H), 3.10 (m, 2H), 4.48 (m, 1H), 4.82 (d, 14Hz, 1H), 5.04 (m, 3H), 5.30 (d, 14Hz, 1H), 5.57 (s, 1H), 6.65 (d, 6Hz, 1H), 7.10-7.45 (m, 15H), 7.62 (m, 1H). FAB-MS: calculated for $\text{C}_{39}\text{H}_{42}\text{N}_4\text{O}_5$ 646; found 669 ($\text{M}+\text{Na}$).

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Step D: N-Ethyl-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

5 To a solution of 74mg (0.114mmol) of the intermediate obtained in Step C in 5mL of dry methanol was added 3 drops of trifluoroacetic acid and 15mg of 20% palladium hydroxide on carbon. The mixture was hydrogenated at room temperature and 10 40psi for 3 hours. The catalyst was removed by filtration through Celite and the solvent removed under vacuum. The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (60:40) to afford 64mg (90%) of the title 15 compound as a white solid. ^1H NMR (200MHz, CD_3OD): 0.85 (t, 7Hz, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 2.1 (m, 1H), 2.3 (m, 1H), 2.50-2.65 (m, 4H), 3.09 (q, 7Hz, 2H), 4.40 (dd; 6, 13Hz; 1H), 4.92 (d, 15Hz, 1H), 20 5.30 (d, 15Hz, 1H), 7.20-7.52 (m, 12H). FAB-MS: calculated for $\text{C}_{31}\text{H}_{36}\text{N}_4\text{O}_3$ 512; found 514 (100%).

Example 73

25 N-Ethyl-4'-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

30 The title compound was prepared from N-ethyl-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

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(Example 72) and D-glyceraldehyde acetonide (used crude as prepared according to the procedure of Hertel, L.W.; Grossman, C. S.; Kroin, J.S., Synth. Comm. 1991, 21, 151-154.) by the procedure described in Example 71. ^1H NMR (200MHz, CD₃OD): 0.87 (t, 7Hz, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 2.10 (m, 1H), 2.35 (m, 1H), 2.50-2.65 (m, 4H), 2.85-3.25 (m, 4H), 3.55 (m, 2H), 3.83 (m, 1H), 4.40 (dd; 8, 12Hz; 1H), 5.00 (d, 15Hz, 1H), 5.25 (d, 15Hz, 1H), 7.20-7.52 (m, 12H). FAB-MS: calculated for C₃₄H₄₂N₄O₅ 586; found 588 (100%).

Example 74

15 N-(2-Hydroxyethyl)-4'--[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

20 Step A: N-(2-Hydroxyethyl)-4'--[3(R)-[3-(benzyloxy-carbonyl)amino-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide To a solution of 70mg (0.11mmol) of

25 4'-[[2,3,4,5-tetrahydro-3(R)-[3-methyl-1-oxo-3-[(benzyloxycarbonyl)amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid (Example 72, Step B) in 2mL of dry methylene chloride under nitrogen at 0°C was added 0.023mL (0.17mmol) of triethylamine followed by 55mg (0.12mmol) of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. After 5

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minutes, 0.010mL (0.12mmol) of ethanolamine was added to the reaction by syringe. The reaction mixture was slowly warmed to room temperature. After 2 hours, the reaction was diluted with 75mL of ethyl acetate, 5 washed with 25mL of 5% aqueous citric acid, 25mL of saturated sodium bicarbonate and 25mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on 10 silica gel eluting with ethyl acetate/methanol (97:3) to afford 58mg (78%) of the product as a white foam.
 ^1H NMR (200MHz, CDCl_3): 1.30 (s, 3H), 1.35 (s, 3H), 1.80 (m, 1H), 2.20-2.75 (m, 7H), 3.10-3.40 (m, 4H), 4.51 (m, 1H), 4.92 (d, 14Hz, 1H), 5.00 (s, 2H), 5.10 (d, 14Hz, 1H), 5.68 (s, 1H), 6.53 (d, 6Hz, 1H), 7.12-7.48 (m, 16H), 7.65 (d; 1, 6Hz; 1H). FAB-MS: calculated for $\text{C}_{39}\text{H}_{42}\text{N}_4\text{O}_6$ 662; found 686 ($\text{M}+\text{Na}$).

Step B: $\text{N}-(2\text{-Hydroxyethyl})-4'-(3(\text{R})-[3\text{-amino}-3-$
20 methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-
2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-
biphenyl]-2-carboxamide, trifluoroacetate
The title compound was prepared from the
intermediate obtained in Step A by the procedure
described in Example 72, Step D. ^1H NMR
25 (200MHz, CD_3OD): 1.35 (s, 3H), 1.39 (s, 3H), 2.00-2.40 (m, 2H), 2.41-2.68 (m, 4H), 3.21 (t, 5Hz, 2H), 3.41 (t, 5Hz, 2H), 4.40 (dd; 6, 10Hz; 1H), 4.95 (d, 15Hz, 1H), 5.26 (d, 15Hz, 1H), 7.20-7.52 (m, 12H). FAB-MS:
30 calculated for $\text{C}_{31}\text{H}_{36}\text{N}_4\text{O}_4$ 528; found 530 (100%).

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Example 75

5 N-(Phenylmethyl)-4'--[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide,
trifluoroacetate

10 Step A: N-(Phenylmethyl)-4'--[[3(R)-[[3-(benzyloxy-carbonyl)amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide

15 The title compound was prepared from
4'-[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxycarbonyl)amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid (Example 72, Step B) and benzylamine according to the procedure described in Example 74, Step A. ¹H NMR (200MHz, CDCl₃): 1.31 (s, 3H), 1.35 (s, 3H), 1.75 (m, 1H), 2.30-2.65 (m, 5H), 4.23 (d, 5Hz, 2H), 4.47 (m, 1H), 4.83 (d, 14Hz, 1H), 5.02 (s, 2H), 5.45 (m, 1H), 5.60 (s, 1H), 6.68 (d, 6Hz, 1H), 6.90 (m, 2H), 7.10-7.50 (m, 20H), 7.65 (m, 1H). FAB-MS: calculated for C₄₄H₄₄N₄O₅ 708; found 709 (M+H), 731 (M+Na, 100%).

25 Step B: N-(Phenylmethyl)-4'--[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

30 The title compound was prepared from the intermediate obtained in Step A according to the procedure described in Example 72, Step D. ¹H NMR (200MHz, CD₃OD): 1.35 (s, 3H), 1.39 (s, 3H), 2.00-2.45

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(m, 2H), 2.48-2.68 (m, 4H), 4.28 (m, 2H), 4.40
(dd; 8, 12Hz; 1H), 4.95 (d, 15Hz, 1H), 5.26 (d, 15Hz, 1H),
7.05 (m, 2H), 7.15-7.55 (m, 15H), 8.47 (t, 6Hz, 1H).
FAB-MS: calculated for C₃₆H₃₈N₄O₃ 574; found 576
5 (100%).

Example 76

10 N-[(4-Methoxyphenyl)methyl]-4'--[[3(R)-[(3-amino-3-
methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-
1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carbox-
amide, trifluoroacetate

15 Step A: N-[(4-Methoxyphenyl)methyl]-4'--[[3(R)-[(3-
(benzyloxycarbonyl)amino-3-methyl-1-oxo-
butyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-
benzazepin-1-yl]methyl][1,1'-biphenyl]-2-
carboxamide

The title compound was prepared from
20 4'--[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-
[(benzyloxyoxy)carbonyl]amino]butyl]amino]-2-oxo-1H-
1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxylic
acid (Example 72, Step B) and 4-methoxybenzylamine by
the procedure described in Example 74, Step A. ¹H
25 NMR (200MHz, CD₃OD): 1.40 (s, 6H), 2.00 (m, 1H), 2.31
(m, 1H), 2.50-2.75 (m, 4H), 3.82 (s, 3H), 4.27 (s, 2H),
4.43 (dd; 7, 11Hz; 1H), 4.95 (d, 15Hz, 1H), 5.05
(d, 12Hz, 1H), 5.15 (d, 12Hz, 1H), 5.37 (d, 15Hz, 1H), 6.87
(m, 3H), 7.03 (d, 8Hz, 2H), 7.20-7.57 (m, 19H). FAB-MS:
30 calculated for C₄₅H₄₆N₄O₆ 738; found 740.

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Step B: N-[(4-Methoxyphenyl)methyl]-4'--[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

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The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 72, Step D. ^1H NMR (200MHz, CD₃OD): 1.32 (s, 3H), 1.37 (s, 3H), 2.00-2.45 (m, 2H), 2.48-2.68 (m, 4H), 3.75 (s, 3H), 4.20 (s, 2H), 4.40 (dd; 8, 12Hz, 1H), 4.95 (d, 14Hz, 1H), 5.25 (d, 14Hz, 1H), 6.80 (d, 8Hz, 2H), 6.97 (d, 8Hz, 2H), 7.19-7.52 (m, 12H). FAB-MS: calculated for C₃₇H₄₀N₄O₄ 604; found 606 (100%).

Example 77

N-[(4-Hydroxyphenyl)methyl]-4'--[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

To a solution of 60.5mg (0.084mmol) of N-[(4-methoxyphenyl)methyl]-4'--[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate (Example 76) in 3mL of dry methylene chloride under nitrogen was added 0.42mL (0.42mmol) of 1.0 M solution of boron tribromide in methylene chloride. The reaction mixture was stirred for 2 hours then 2mL of water was added followed by sufficient methanol to dissolve any remaining precipitate. The solvent was removed under vacuum.

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The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/ 0.1% aqueous trifluoroacetic acid (60:40) to afford 53mg (89%) of the title compound as a white solid. ^1H NMR (200MHz, CD₃OD): 1.39 (s, 3H), 1.45 (s, 3H), 2.10-2.50 (m, 2H), 2.52-2.72 (m, 4H), 4.23 (s, 2H), 4.48 (dd; 8, 12Hz; 1H), 5.02 (d, 14Hz, 1H), 5.30 (d, 14Hz, 1H), 6.72 (d, 8Hz, 2H), 6.94 (d, 8Hz, 2H), 7.20-7.57 (m, 12H). FAB-MS: calculated for C₃₆H₃₈N₄O₄ 590; found 592 (100%).

Example 78

15 N,N-Diethyl-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-y1]-methyl][1,1'-biphenyl]-2-carboxamide. trifluoroacetate

Step A: N,N-Diethyl-4'-[[3(R)-[[3-(benzyloxycarbonyl)amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-y1]methyl][1,1'-biphenyl]-2-carboxamide
20 Prepared from 4'-[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxy)carbonyl]amino]butyl]-amino]-2-oxo-1H-1-benzazepin-1-y1]methyl][1,1'-biphenyl]-2-carboxylic acid (Example 72, Step B) and diethylamine according to the procedure described in Example 74, Step A. ^1H NMR (200MHz, CDCl₃): 0.65 (t, 6Hz, 3H), 0.72-1.00 (m, 3H), 1.35 (s, 6H), 1.96 (m, 1H), 2.27 (m, 1H), 2.40-2.68 (m, 6H), 2.80-3.12 (m, 2H), 3.55 (m, 1H), 4.35 (dd; 6, 10Hz; 1H), 4.82 (dd, 6, 15Hz; 1H), 5.04 (dd; 9, 16Hz; 2H), 5.40 (dd; 8, 14Hz; 1H), 7.15-7.55 (m, 17H). FAB-MS: calculated for C₄₁H₄₆N₄O₅ 674; found 676, 698 (M+Na).

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Step B: N,N-Diethyl-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

5 The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 72, Step D. ^1H NMR (200MHz, CD_3OD): 0.67 (t, 7Hz, 3H), 0.75-1.00 (m, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 2.00-2.80 (m, 7H), 2.80-3.15 (m, 2H), 3.55 (m, 1H), 4.40 (dd; 7, 12Hz; 1H), 4.87 (d, 15Hz, 1H), 5.36 (d, 15Hz, 1H), 7.20-7.55 (m, 12H).
10 FAB-MS: calculated for $\text{C}_{33}\text{H}_{40}\text{N}_4\text{O}_3$ 540; found 542 (100%).

15 Example 79

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carboxy[1,1'-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide. trifluoroacetate

To a slurry of 54 mg (0.086mmol) of
4' - [[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-
[(benzyloxycarbonyl)amino]butyl]amino]-2-oxo-1H-1-
benzazepin-1-yl)methyl][1,1'-biphenyl]-2-carboxylic
acid (Example 72, Step B) in 2mL of dry methylene
chloride under nitrogen was added 0.5mL (0.5mmol) of
1.0M solution of boron tribromide in methylene
chloride. The reaction mixture was stirred at room
temperature for 30 minutes then quenched by the
addition of 2mL of water. The remaining solids were
dissolved by the addition of 2mL of methanol and the
solvent were removed under vacuum. The resulting

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material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (60:40) to afford 38mg (74%) of the title compound as an off-white solid. ^1H NMR (200MHz, CD₃OD): 1.34 (s, 3H), 1.39 (s, 3H), 2.00-2.46 (m, 2H), 2.50-2.70 (m, 4H), 4.42 (dd; 7, 11Hz; 1H), 4.99 (d, 14Hz, 1H), 5.23 (d, 14Hz, 1H), 7.2-7.6 (m, 11H), 7.76 (dd; 1, 7Hz; 1H). FAB-MS: calculated for C₂₉H₃₁N₃O₄ 485; found 486 (M+H, 100%).

Example 80

15 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide, trifluoroacetate

Step A: 3-[(Benzylloxycarbonyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide

To a solution of 124mg (0.20mmol) of 4'-[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzylloxycarbonyl)amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid (Example 72, Step B) in 1.5mL of dry 1,2-dimethoxyethane at 0°C was added 0.046mL (0.421mmol) of N-methylmorpholine followed by 0.055mL (0.42mmol) of isobutyl chloroformate. The reaction mixture was stirred at 0°C for 1 hour then filtered. Solids were rinsed with 1,2-dimethoxyethane (2x1mL)

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and the filtrates combined. To the filtrate at 0°C was added by syringe a solution of 30.3mg (0.801mmol) of sodium borohydride in 0.3mL of water. The reaction mixture was stirred at 0°C for 15 minutes then diluted with ethyl acetate (75mL). The organic layer was washed with saturated aqueous ammonium chloride (25mL) and brine (25mL), then dried over magnesium sulfate, filtered and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/hexane (75:25) to afford 86mg (71%) of the product as a white solid. ^1H NMR (200MHz, CDCl_3): 1.35 (s, 3H), 1.37 (s, 3H), 2.80 (m, 2H), 2.50 (m, 4H), 4.50 (m, 3H), 4.90 (d, 15Hz, 1H), 5.03 (dd; 10, 12Hz; 2H), 5.18 (d, 15Hz, 1H), 5.77 (s, 1H), 6.70 (d, 8Hz, 1H), 7.10-7.40 (m, 16H), 7.53 (m, 1H). FAB-MS: calculated for $\text{C}_{37}\text{H}_{39}\text{N}_3\text{O}_5$ 605; found 607 (30%).

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide, trifluoroacetate

To a solution of 40mg (0.066mmol) of the intermediate obtained in Step A in 2mL of methanol was added 5mg of 20% palladium hydroxide on carbon catalyst. The resulting mixture was hydrogenated at room temperature and 1 atmosphere for 30 minutes. The catalyst was removed by filtration through Celite and the solvent removed under vacuum. The residue was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/ 0.1%

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aqueous trifluoroacetic acid (60:40) to afford 36mg (95%) of the title compound as a white solid. ^1H NMR (200MHz, CD₃OD): 1.34 (s, 3H), 1.37 (s, 3H), 2.0-2.7 (m, 6H), 4.44 (m, 3H), 4.95 (d, 15Hz, 1H), 5.25 (d, 15Hz, 1H), 7.1-7.5 (m, 11H), 7.55 (d, 6Hz, 1H).
5 FAB-MS: calculated for C₂₉H₃₃N₃O₃ 471; found 472 (M+H, 100%).

Example 81

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3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[(2'-methyl[1,1'-biphenyl]-4-yl)methyl]-1H-benzazepin-3(R)-yl]butanamide, trifluoroacetate

To a solution of 30mg (0.066mmol) of
15 3-[(benzyloxycarbonyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl)methyl]-1H-benzazepin-3(R)-yl]butanamide (Example 80, Step A) in 2mL of methanol was added 5mg of 20% palladium hydroxide on carbon catalyst and 1 drop of trifluoroacetic acid. The resulting mixture was hydrogenated at room temperature and 1 atmosphere for 4 hours. The catalyst was removed by filtration through Celite and the solvent removed under vacuum. The residue was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/ 0.1% aqueous trifluoroacetic acid (65:35) to afford 30mg (100%) of the title compound as a white solid. ^1H NMR (200MHz, CD₃OD): 1.35 (s, 3H), 1.40 (s, 3H), 2.0-2.7 (m, 6H), 2.10 (s, 3H), 4.42 (dd, 8, 12Hz; 1H), 4.95 (d, 14Hz, 1H), 5.27 (d, 14Hz, 1H), 7.1-7.4 (m, 12H). FAB-MS: calculated for C₂₉H₃₃N₃O₂ 455; found 456 (M+H, 100%).

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Example 82

5 4'-[[3(R)-[[3-[(2(S),3(S),4-Trihydroxybutylamino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl)methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

Step A: 1-t-Butyldimethylsilyl-2,3-isopropylidene-D-threitol

10 To a solution of 1.0g (6.2mmol) of 2,3-isopropylidene-D-threitol in 6.0mL of dry dimethylformamide at 0°C was added 0.44g (6.5mmol) of imidazole followed by dropwise addition of a solution of 0.93g (6.2mmol) of t-butyldimethylsilyl chloride in 6.0mL of dimethylformamide. The reaction mixture was stirred at 0°C for 30 minutes then at room temperature for 1 hour. The reaction mixture was poured into 75mL water and extracted with ether (3x75mL). The combined ether extracts were washed with saturated aqueous sodium bicarbonate and with brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The resulting oil was purified by flash chromatography on silica gel, eluting with hexanes/ethyl acetate (75:25) to afford 0.70g (41%) of product as a clear oil. ^1H NMR (200MHz, CDCl_3): 0.07 (s, 6H), 0.90 (s, 9H), 1.39 (s, 3H), 1.41 (s, 3H), 3.60-4.00 (m, 7H). FAB-MS: calculated for $\text{C}_{13}\text{H}_{28}\text{O}_4\text{Si}$ 276; found 261 (M-15, 10%).

30

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Step B: 5(S)-t-Butyldimethylsilyloxyethyl-2,2-dimethyl-1,3-dioxolan-4(R)-carboxaldehyde

To a solution of 0.676g (2.44mmol) of the intermediate obtained in Step A in 35mL of dry methylene chloride was added 3mL of dry dimethylsulfoxide followed by 2.8mL (20.2mmol) of triethylamine. To this solution was added 1.61g (10.1mmol) of pyridine sulfur trioxide complex in three portions over a 5 minute period. The reaction mixture was stirred at room temperature for 2 hours at which time it was diluted with 250mL of ethyl acetate. The mixture was transferred to a separatory funnel and washed with 1N HCl (2x50mL), saturated aqueous sodium bicarbonate (50mL) and brine (50mL). The organic layer was dried over magnesium sulfate, filtered, and the solvent removed under vacuum to afford 672mg (100%) of product which was used in the next reaction without further purification. ^1H NMR (200MHz, CDCl_3): 0.09 (s, 6H), 0.87 (s, 9H), 1.40 (s, 3H), 1.45 (s, 3H), 3.78 (d, 4Hz, 2H), 4.10 (m, 1H), 4.30 (dd; 2, 6Hz; 1H), 9.85 (d, 2Hz, 1H).

Step C: 4'-[[3(R)-[[3-[(2(S),3(S),4-Trihydroxybutyl-amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from 4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

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(Example 69) and the intermediate obtained in Step B by the procedure described in Example 71. ^1H NMR (200MHz, CD₃OD): 1.37 (s, 3H), 1.41 (s, 3H), 2.12-2.40 (m, 2H), 2.55-2.71 (m, 4H), 3.05-3.25 (m, 2H), 3.59 (m, 3H), 3.92 (m, 1H), 4.40 (dd; 7, 12Hz; 1H), 5.02 (d, 15Hz, 1H), 5.15 (d, 15Hz, 1H), 7.20-7.58 (m, 12H). FAB-MS: calculated for C₃₃H₄₀N₄O₆ 588; found 589 (M+H, 70%).

10

Example 83

4'-[[3(R)-[(2(R)-Amino-3-hydroxy-1-oxopropyl)amino]-

2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-

[1,1'-biphenyl]-2-carboxamide, trifluoroacetate

15

Step A: 2(R)-t-Butoxycarbonylamino-3-(t-butoxy)-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]propanamide

To a solution of 200mg (1.13mmol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (Example 1, Step B) in 8mL of dry methylene chloride was added 0.206mL (1.48mmol) of triethylamine, 553mg (1.25mmol) of BOC-D-serine t-butyl ether followed by 602mg (1.36mmol) of benzotriazol-1-yloxytris(dimethyl-amino)phosphonium hexafluorophosphate. The reaction mixture was stirred at room temperature for 2 hours then diluted with 100mL of ethyl acetate, washed with 25mL of 5% aqueous citric acid, 25mL of saturated sodium bicarbonate and 25mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvents removed under vacuum. The residue was

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purified by flash chromatography on silica gel,
eluting with ethyl acetate/hexane (55:45) to afford
480mg (100%) of the product as a white foam. ^1H NMR
(200MHz, CDCl_3): 1.20 (s, 9H), 1.47 (s, 9H), 1.92
5 (m, 1H), 2.55-3.02 (m, 3H), 3.38 (t, 8Hz, 1H), 3.78
(m, 1H), 4.15 (m, 1H), 4.52 (m, 1H), 5.45 (s, 1H), 7.00
(m, 1H), 7.10-7.35 (m, 3H), 7.68 (d, 4Hz, 1H), 8.05
(s, 1H). FAB-MS: calculated for $\text{C}_{22}\text{H}_{33}\text{N}_3\text{O}_5$ 419;
found 420 ($\text{M}+\text{H}$, 20%), 426 ($\text{M}+\text{Li}$, 40%).

10

Step B: 2(R)-t-Butoxycarbonylamino-3-(t-butoxy)-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-cyano[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]propanamide

15

Prepared from the intermediate obtained in Step A and 4'-bromomethyl-1,1'-biphenyl-2-nitrile (Example 69, Step C) by the procedure described in Example 69, Step D. ^1H NMR (200MHz, CDCl_3): 1.20 (s, 9H), 1.47 (s, 9H), 1.88 (m, 1H), 2.45-2.75 (m, 3H), 3.38 (dd, 6,8Hz; 1H), 3.78 (m, 1H), 4.15 (m, 1H), 4.52 (m, 1H), 4.97 (d, 14Hz, 1H), 5.21 (d, 14Hz, 1H), 5.40 (s, 1H), 7.1-7.5 (m, 11H), 7.6-7.8 (m, 2H). FAB-MS: calculated for $\text{C}_{36}\text{H}_{42}\text{N}_4\text{O}_5$ 610; found 618 ($\text{M}+\text{Li}$, 30%).

20

Step C: 4'-[[3(R)-[[2(R)-(t-Butoxycarbonyl)amino-3-hydroxy-1-oxopropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide

25

Prepared from the intermediate obtained in Step B by the procedure described in Example 69, Step E. ^1H NMR (400MHz, CDCl_3): 1.18 (s, 9H), 1.45

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(s, 9H), 1.85 (m, 1H), 2.45 (m, 1H), 2.62 (m, 2H), 3.38
5 (dd; 6, 8Hz; 1H), 3.72 (m, 1H), 4.12 (m, 1H), 4.47 (m, 1H),
4.92 (d, 14Hz, 1H), 5.13 (s, 1H), 5.20 (d, 14Hz, 1H), 5.37
(s, 2H), 7.17 (m, 3H), 7.2-7.4 (m, 6H), 7.40 (m, 1H),
10 7.47 (m, 1H), 7.60 (s, 1H), 7.72 (d, 8Hz, 1H). FAB-MS:
calculated for $C_{36}H_{44}N_4O_6$ 628; found 636 (M+Li, 40%).

Step D: 4'-[3(R)-[(2(R)-Amino-3-hydroxy-1-oxo-propyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 69, Step F. 1H NMR (200MHz, CD₃OD): 2.10 (m, 1H), 2.37 (m, 1H), 2.62 (m, 2H), 3.8-4.1 (m, 3H), 4.42 (dd; 6, 11Hz; 1H), 4.95 (d, 14Hz, 1H), 5.27 (d, 14Hz, 1H), 7.2-7.6 (m, 12H). FAB-MS: calculated for $C_{27}H_{28}N_4O_4$ 472; found 473 (M+H, 100%).

20

Example 84

4'-[3(R)-[(2-Amino-2-methyl-1-oxopropyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

30

Step A: 2-t-Butoxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-cyano[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

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Prepared from 2-t-butoxycarbonylamino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]propanamide (Example 63, Step A) and 4'-bromomethyl-1-1'-biphenyl-2-nitrile (Example 69, Step C) by the procedure described in Example 69, Step D. ^1H NMR (200MHz, CDCl_3): 1.39 (s, 9H), 1.41 (s, 3H), 1.45 (s, 3H), 1.83 (m, 1H), 2.4-2.8 (m, 3H), 4.48 (m, 1H), 4.90 (d, 16Hz, 1H), 4.93 (s, 1H), 5.22 (d, 16Hz, 1H), 7.1-7.5 (m, 10H), 7.60 (m, 1H), 7.72 (d, 6Hz, 1H). FAB-MS: calculated for $\text{C}_{33}\text{H}_{36}\text{N}_4\text{O}_4$ 552; found 554 (20%).

Step B: 4'-[[3(R)-[[2-(t-Butoxycarbonyl)amino-2-methyl-1-oxopropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide

Prepared from the intermediate obtained in Step A by the procedure described in Example 69, Step E. ^1H NMR (200MHz, CDCl_3): 1.40 (s, 12H), 1.43 (s, 3H), 1.83 (m, 1H), 2.4-2.8 (m, 3H), 4.48 (m, 1H), 4.85 (d, 14Hz, 1H), 4.97 (s, 1H), 5.20 (s, 1H), 5.22 (d, 14Hz, 1H), 5.57 (s, 1H), 7.1-7.5 (m, 11H), 7.70 (dd, 1, 6Hz; 1H).

Step C: 4'-[[3(R)-[(2-Amino-2-methyl-1-oxopropyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 69, Step F. ^1H NMR

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(200MHz, CD₃OD): 1.52 (s, 3H), 1.65 (s, 3H), 2.25
10 (m, 2H), 2.60 (m, 2H), 4.40 (m, 1H), 5.00 (d, 7Hz, 1H),
5.20 (d, 7Hz, 1H), 7.2-7.6 (m, 12H). FAB-MS:
calculated for C₂₈H₃₀N₄O₃ 470; found 471 (M+H, 100%).

5

Example 85

10 3-(2-Aminoethyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carboxy[1,1'-biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-yl]butanamide, dihydrochloride

15 Step A: 4'-[[2,3,4,5-Tetrahydro-3(R)-[[3-methyl-1-oxo-3-amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxylic acid, 1,1-dimethylethyl ester, acetate

20 To a solution of 400mg (0.592mmol) of
4'-[[2,3,4,5-tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxycarbonyl)amino]butyl]amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxylic
acid 1,1-dimethylethyl ester (Example 72, Step A) in
10mL of methanol was added 0.034mL (0.59mmol) of
acetic acid and 80mg of 20% palladium hydroxide on
carbon catalyst. The resulting mixture was
25 hydrogenated at room temperature and 1 atmosphere for
4 hours. The catalyst was removed by filtration
through Celite and the filtrate concentrated under
vacuum to afford 345mg (97%) of the product as a
white solid. ¹H NMR (400MHz, CD₃OD): 1.17 (s, 9H),
30 1.35 (s, 3H), 1.42 (s, 3H), 1.95 (s, 3H), 2.15 (m, 1H),
2.35 (m, 1H), 2.50 (d, 12Hz, 1H), 2.5-2.78 (m, 3H), 4.42

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(dd; 8, 11Hz, 1H), 5.02 (d, 15Hz, 1H), 5.37 (d, 15Hz, 1H),
7.1-7.6 (m, 11H), 7.67 (d, 8Hz, 1H). FAB-MS:
calculated for C₃₃H₃₉N₃O₄ 541; found 542 (M+H, 100%).

5 Step B: 2-(t-Butoxycarbonylamino)acetaldehyde
To a solution of 700mg (4.34mmol) of
2-(t-butoxycarbonylamino)ethanol in 35mL of dry
methylene chloride was added 4.0mL of dimethyl-
sulfoxide and 4.8mL (35mmol) of triethylamine,
10 followed by 2.8g (17mmol) of pyridine sulfur trioxide
complex in three portions over 5 minutes. The
reaction was stirred at room temperature for 3 hours
then diluted with 500mL of ether. The mixture was
transferred to a separatory funnel and washed with 1N
15 HCl (2x50mL), saturated aqueous sodium bicarbonate
(100mL), and brine (100mL). The organic layer was
dried over magnesium sulfate, filtered, and the
solvent removed under vacuum to afford 550mg (80%) of
product which was used without further purification.
20 ¹H NMR (200MHz, CDCl₃): 1.40 (s, 9H), 4.05 (d, 7Hz, 2H),
5.17 (s, 1H), 9.62 (s, 1H).

25 Step C: 3-(2-Aminoethyl)amino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-carboxy-[1,1'-
biphenyl]-4-yl]methyl]-1H-benzazepin-3(R)-
yl]butanamide, dihydrochloride
To a solution of 345mg (0.573mmol) of the
intermediate obtained in Step A in 10mL of dry
methanol was added 0.088mL (0.63mmol) of
30 triethylamine, 3.4g of dry 4A powdered molecular
sieves followed by a solution of 540mg (3.4mmol) of

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2-(t-butoxycarbonylamino)acetaldehyde (Step B) in 5mL of dry methanol. The pH of the mixture was carefully adjusted to 6.5 with glacial acetic acid (7 drops).
5 The reaction was stirred for 3 hours at which time 3.4mL (3.4mmol) of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran was added by syringe. The reaction was stirred for 20 hours then filtered through a pad of Celite. To the filtrate was added 2.0mL of acetic acid (CAUTION! evolution
10 of hydrogen cyanide). The resulting mixture was stirred for 3 hours. The solvent was removed under vacuum to afford a clear oil which was dissolved in 5mL of methylene chloride. To this solution was added 5 drops of anisole followed by 5mL of
15 trifluoroacetic acid. The mixture was stirred for 4 hours at room temperature then all volatiles removed under vacuum to give an oil which was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (55:45). The product thus
20 obtained was converted to its dihydrochloride salt by dissolving it in 10mL of 6 N HCl followed by evaporation under vacuum. The cycle was repeated three times to afford 273mg (79%) of the title
25 compound as an off-white solid. ^1H NMR (200MHz,CD₃OD): 1.45 (s,3H), 1.51 (s,3H), 2.1-2.5 (m,2H), 2.5-2.7 (m,4H), 3.2-3.5 (m,4H), 4.42 (dd;8,11Hz;1H), 5.00 (d,15Hz,1H), 5.22 (d,15Hz,1H), 7.2-7.6 (m,11H), 7.78 (d,6Hz,1H). FAB-MS:
30 calculated for C₃₁H₃₆N₄O₄ 528; found 529 (M+H,100%).

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Example 86

3-[(2(S)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Step A: 3-[(2-(S)-Benzyl oxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

To a solution of 0.20g (0.34mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1) in 8mL of dry methanol was added 0.096mL (2.50mmol) of triethylamine, 1.0g of dry 4A powdered molecular sieves followed by a solution of 0.296g (1.80mmol) of (S)-2-benzyl oxypropanal (prepared from ethyl-L-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett. 1985, 26, 1261-1264.) in 2mL of dry methanol. The pH of the mixture was carefully adjusted to 6.5 with glacial acetic acid. The reaction was stirred for 2 hours at which time 2.06mL (2.06mmol) of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran was added by syringe. The reaction was stirred for 24 hours then filtered through a pad of Celite. To the filtrate was added 5.0mL of trifluoroacetic acid (CAUTION! evolution of hydrogen cyanide) and the

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resulting mixture was stirred for three hours. The solvent was removed under vacuum to afford 1.6g of a clear oil which was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (65:35) to afford 254mg (100%) of the product as a white solid.
5 ¹H NMR (200MHz,CD₃OD): 1.28 (d,6Hz,3H), 1.35 (s,3H), 1.40 (s,3H), 2.10 (m,1H), 2.2-2.7 (m,5H), 2.95 (m,1H), 3.20 (m,1H), 3.83 (m,1H), 4.42 (m,1H), 4.50 (d,11Hz,1H), 4.63 (d,11Hz,1H), 5.20 (d,15Hz,1H), 6.95 (d,8Hz,2H), 7.1-7.7 (m,15H). FAB-MS: calculated for C₃₉H₄₃N₇O₃ 657; found 658 (M+H,100%).
10

15 Step B: 3-[(2(S)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

20 A solution of 250mg (0.324mmol) of the intermediate prepared in Step A in 5mL of methanol was placed in a shaker bottle. To the solution was added 3 drops of trifluoroacetic acid and 0.1g of 30% palladium on carbon. The mixture was hydrogenated at room temperature and 40psi for 3 days. The catalyst
25 was removed by filtration through Celite and the filtrate evaporated under vacuum. The resulting material was purified by reverse phase medium pressure liquid chromatography on C-8 eluting with methanol/0.1% aqueous trifluoroacetic acid (60:40) to afford 149mg (64%, Steps A + B) of the title compound
30

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as a white solid. ^1H NMR (200MHz, CD₃OD): 1.20 (d, 6Hz, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 2.10 (m, 1H), 2.2-2.6 (m, 5H), 2.78 (m, 1H), 3.08 (m, 1H), 3.92 (m, 1H), 4.35 (dd; 7, 10Hz; 1H), 4.95 (d, 14Hz, 1H), 5.18 (d, 14Hz, 1H), 7.00 (d, 8Hz, 2H), 7.1-7.4 (m, 6H), 7.5-7.7 (m, 4H). FAB-MS: calculated for C₃₂H₃₇N₇O₃ 567; found 568 (M+H, 100%).

Example 87

10

3-[[2-(t-Butoxycarbonylamino)ethyl]amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, trifluoroacetate

15

To a solution of 485mg (0.833mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, trifluoroacetate (Example 1) in 8mL of dry methanol was added 0.232mL

20

(1.67mmol) of triethylamine, 2.5g of dry 4A powdered molecular sieves followed by a solution of 200mg (1.25mmol) of 2-(t-butoxycarbonylamino)acetaldehyde (Example 85, Step B) in 1mL of dry methanol. The pH of the mixture was carefully adjusted to 6.5 with

25

glacial acetic acid. The reaction was stirred for 2 hours at which time 5.0mL (5.0mmol) of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran was added by syringe. The reaction was stirred for 20 hours then filtered through a pad of Celite.

30

To the filtrate was added 1.0mL of acetic acid (CAUTION! evolution of hydrogen cyanide). The

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resulting mixture was stirred for 30 minutes. The solvent was removed under vacuum to afford a clear oil which was purified by reverse phase high pressure liquid chromatography on C-18 eluting with
5 methanol/0.1% aqueous trifluoroacetic acid (65:35) to afford 347mg (54%) of the title compound as a white solid. ^1H NMR (200MHz, CD₃OD): 1.30 (s, 9H), 1.35 (s, 3H), 1.39 (s, 3H), 2.10 (m, 1H), 2.2-2.6 (m, 5H), 3.10 (m, 2H), 3.35 (m, 2H), 4.39 (dd; 8, 11Hz; 1H), 4.95 (d, 15Hz, 1H), 5.21 (d, 15Hz, 1H), 7.05 (m, 2H), 7.2-7.5 (m, 7H), 7.5-7.7 (m, 3H). FAB-MS: calculated for C₃₆H₄₄N₈O₄ 652; found 654 (100%).

Example 88

15

3-[(2-Aminoethyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, di(trifluoroacetate)

20

The title compound was prepared from 3-[(2-t-butoxycarbonylamino)ethyl]amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, monotrifluoroacetate (Example 87) by the procedure described in Example 69, Step F. ^1H NMR (200MHz, CD₃OD): 1.38 (s, 3H), 1.42 (s, 3H), 2.12 (m, 1H), 2.2-2.7 (m, 5H), 3.33 (m, 4H), 4.35 (dd; 6, 11Hz; 1H), 4.85 (d, 15Hz, 1H), 5.21 (d, 15Hz, 1H), 7.00 (d, 8Hz, 2H), 7.1-7.4 (m, 7H), 7.5-7.7 (m, 3H).

25

FAB-MS: calculated for C₃₁H₃₆N₈O₂ 552; found 553 (M+H, 100%).

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Example 89

5 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-
[1-(carboxymethyl)tetrazol-5-yl][1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,
trifluoroacetate

10 Step A: 3-(t-Butoxycarbonylamino)-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-
(carboxymethyl)tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-
y1]-butanamide, t-butyl ester
and,

15 3-(t-Butoxycarbonylamino)-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(2-
(carboxymethyl)tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-
y1]-butanamide, t-butyl ester

20 To a solution of 101mg (0.166mmol) of
3-(t-butoxycarbonylamino)-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-
butanamide (Example 16, Step A) in 1mL of acetone was
added 0.028mL (0.20mmol) of triethylamine followed by
25 dropwise addition of 0.029mL (0.18mmol) of t-butyl
bromoacetate. The reaction mixture was stirred at
room temperature for 1 hour then the solvent was
removed under vacuum. The residue was dissolved in
50mL of methylene chloride, washed with saturated
30 aqueous sodium bicarbonate, dried over magnesium
sulfate and filtered. The filtrate was evaporated

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under vacuum to afford 139mg (100%) of product as a mixture of N-1 and N-2 tetrazole isomers. ^1H NMR of mixture (200MHz, CDCl_3): 1.30 (s, 6H), 1.40 (s, 6H), 1.50 (m, 36H), 1.90 (m, 2H), 2.4-2.7 (m, 8H), 3.80 (s, 2H), 4.07 (s, 2H), 4.52 (m, 2H), 4.80 (m, 2H), 5.37 (m, 2H), 6.72 (m, 2H), 7-0-7.4 (m, 16H), 7.4-7.8 (m, 6H). FAB-MS calculated for $\text{C}_{40}\text{H}_{49}\text{N}_7\text{O}_6$ 723; found 724 ($\text{M}+\text{H}$, 20%).

- 10 Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-(carboxymethyl)tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate
Prepared from the intermediate obtained in
- 15 Step A by the procedure described in Example 69, Step F. Separation of isomers by reverse phase high pressure liquid chromatography on C-18 eluting with methanol/0.1% aqueous trifluoroacetic acid afforded the title compound in addition to the N-2 isomer. ^1H
- 20 NMR (200MHz, CD_3OD): 1.39 (s, 3H), 1.42 (s, 3H), 2.0-2.7 (m, 6H), 4.40 (dd, 8, 11Hz; 1H), 4.48 (s, 2H), 4.85 (d, 15Hz, 1H), 5.35 (d, 15Hz, 1H), 7.05 (d, 8Hz, 2H), 7.2-7.4 (m, 7H), 7.5-7.9 (m, 3H). FAB-MS: calculated for $\text{C}_{31}\text{H}_{33}\text{N}_7\text{O}_4$ 567; found 568 ($\text{M}+\text{H}$, 100%).
- 25

Example 90

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-(carboxymethyl)tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

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The title compound was prepared from
3-(t-butoxycarbonylamino)-3-methyl-N-[2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(carboxymethyl)-tetrazol-5-y1]-
[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-
5 y1]-butanamide, t-butyl ester (Example 89, Step A) by
the procedure described in Example 89, Step B. ¹H
NMR (200MHz, CD₃OD): 1.35 (s,3H), 1.42 (s,3H),
2.0-2.6 (m,6H), 4.39 (dd;7,11Hz;1H), 4.90
(d,14Hz,1H), 5.20 (d,14Hz,1H), 5.42 (s,2H), 7.04
10 (d,6Hz,2H), 7.15 (d,6Hz,2H), 7.2-7.6 (m,7H), 7.75
(m,1H). FAB-MS: calculated for C₃₁H₃₃N₇O₄ 567;
found 568 (M+H,100%).

Example 91

15

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2,5-dioxo-1-
[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-y1]methyl]-
1H-1-benzazepin-3-y1]-butanamide, trifluoroacetate

20

Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[2,3,4,5-
tetrahydro-2,5-dioxo-1H-1-benzazepin-3-y1]-
butanamide

25

To a solution of 120mg (0.531mmol) of
3-t-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1-
benzazepin-2,5-dione (prepared by the procedure of F.
Stewart, Australian J. Chem. 1980, 33, 633-640.) in
2mL of methanol was added 2mL of 9 N hydrochloric
acid. The mixture was stirred at room temperature
for 24 hours and solvent was removed under vacuum.

30

To the resulting solid in 3mL of dry
methylene chloride was added 0.22mL (1.6mmol) of

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triethylamine, 115mg (0.531mmol) of 3-t-butoxy-carbonylamino-3-methyl butanoic acid (Example 31, Step E) followed by 235mg (0.531mmol) of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. The reaction mixture was stirred at room temperature for 2 hours. The reaction was diluted with 75mL of ethyl acetate, washed with 25mL of 5% aqueous citric acid, 25mL of saturated aqueous sodium bicarbonate and 25mL of brine. The organic layer was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate/hexanes (65:35) to afford 109mg (51%) of the product as a white foam. ^1H NMR (200MHz, CDCl_3): 1.33 (s, 3H), 1.39 (s, 12H), 2.49 (d, 12Hz, 1H), 2.75 (d, 12Hz, 1H), 2.9 (m, 1H), 3.27 (dd; 2, 16Hz; 1H), 5.05 (m, 2H), 7.05 (t, 6Hz, 1H), 7.24 (t, 6Hz, 1H), 7.50 (m, 1H), 7.82 (dd; 2, 8Hz; 1H), 8.85 (s, 1H). FAB-MS: calculated for $\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_5$ 389; found 390 ($\text{M}+\text{H}$, 60%).

Step B: 3-(t-Butoxycarbonylamino)-3-methyl-N-[2,3,-
4,5-tetrahydro-2,5-dioxo-1-[[2'-(N-triphenyl-
25 methyl)tetrazol-5-yl][1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3-yl]butanamide
Prepared from the intermediate obtained in
Step A and N-triphenylmethyl-5-[2-(4'-bromomethyl-
biphen-4-yl)] tetrazole (Example 1, Step J) by the
procedure described in Example 1, Step K. ^1H NMR
30 (200MHz, CDCl_3): 1.35 (s, 3H), 1.40 (s, 12H), 2.49
(d, 14Hz, 1H), 2.6-2.9 (m, 2H), 3.27 (m, 1H), 4.82

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(d,15Hz,1H), 4.92 (d,15Hz,1H), 5.05 (s,1H), 5.15
(m,1H), 6.8-7.6 (m,26H), 7.90 (m,1H). FAB-MS:
calculated for C₅₃H₅₁N₇O₅ 865; found 873 (M+Li).

5 Step C: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-
2,5-dioxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-
yl]butanamide, trifluoroacetate

10 To a solution of 68mg (0.078mmol) of the
intermediate obtained in Step B in 3mL of methanol
was added 14mg of palladium hydroxide catalyst. The
mixture was hydrogenated at room temperature and 1
atmosphere for 20 hours at which time the solids were
filtered and the solvent removed under vacuum.

15 The resulting solid was dissolved in 3mL of
methylene chloride. To this solution was added 3
drops of anisole followed by 2mL of trifluoroacetic
acid. The reaction mixture was stirred for 2 hours
at room temperature, then all volatiles removed under
20 vacuum. The resulting material was purified by
reverse phase high pressure liquid chromatography on
C-18, eluting with methanol/0.1% aqueous trifluoro-
acetic acid (linear gradient; 50% methanol increased
to 55% methanol over 12 minutes) to afford 16.5mg
25 (33%) of the title compound as a white solid. ¹H NMR
(200MHz,CD₃OD): 1.37 (s,3H), 1.40 (s,3H), 2.59
(dd;14,16Hz;2H), 2.9-3.2 (m,2H), 4.97 (d,15Hz,1H),
5.17 (dd;4,12Hz;1H), 5.25 (d,15Hz,1H), 7.00
(d,8Hz,2H), 7.12 (d,8Hz,2H), 7.37 (m,2H), 7.4-7.7
30 (m,6H). FAB-MS: calculated for C₂₉H₂₉N₇O₃ 523;
found 524 (M+H,100%).

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Example 92

5 3-Amino-3-methyl-N-[5-hydroxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3-yl]-butanamide,
trifluoroacetate

10 To a solution of 23mg (0.036mmol) of
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2,5-dioxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H
15 -1-benzazepin-3-yl]-butanamide, trifluoroacetate
(Example 91) in 1mL of methanol/water (4:1) was added
14mg (0.36mmol) of sodium borohydride. The reaction
mixture was stirred for 1 hour then quenched by the
addition of 5 drops of trifluoroacetic acid. The
solvent was removed under vacuum and the resulting
15 material was purified by reverse phase high pressure
liquid chromatography on C-18 eluting with
methanol/0.1% aqueous trifluoroacetic acid (55:45) to
afford 18mg (78%) of the title compound as a white
20 solid. ^1H NMR (200MHz,CD₃OD): 1.37 (s,3H), 1.40
(s,3H), 2.17 (m,1H), 2.3-2.6 (m,3H), 4.30
(dd;8,10Hz;1H), 4.67 (dd;6,10Hz;1H), 4.95
(d,15Hz,1H), 5.23 (d,15Hz,1H), 7.00 (d,8Hz,2H), 7.20
(d,8Hz,2H), 7.35 (m,3H), 7.5-7.7 (m,5H). FAB-MS:
25 calculated for C₂₉H₃₁N₇O₃ 525; found 526 (M+H,100%).

Example 93

30 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-
2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-
[1,1'-biphenyl]-2-thioamide, trifluoroacetate

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Step A: 4'-[3(R)-[(3-t-Butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-thioamide

5 A solution of 380mg (0.67mmol) of 3-[[1-
[[2'-cyano-[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-
tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-
dimethyl-3-oxopropylcarbamic acid, 1,1-dimethylethyl
10 ester (Example 69, Step D), in 5mL of pyridine was
placed in a bomb and treated with 5mL of
triethylamine and excess hydrogen sulfide was
introduced under pressure. The bomb was sealed and
heated for 12 hours at 90°C. The bomb was vented
into 5 M sodium hydroxide and the contents poured
15 into 40mL of water, then extracted with ether (3x).
The combined extracts were washed with water (3x),
dried over magnesium sulfate, filtered and evaporated
under vacuum to afford 330mg (0.53mmol, 82%) of
product. ^1H NMR (200MHz, CDCl_3): 1.38 (s, 6H), 1.45
20 (s, 9H), 1.90 (m, 1H), 2.4-2.7 (m, 4H), 2.92 (m, 1H),
4.55 (m, 1H), 4.94 (d, 15Hz, 1H), 5.22 (d, 15Hz, 1H), 5.31
(br s, 1H), 6.50 (br s, 1H), 6.70 (m, 1H), 7.1-7.5
(m, 12H), 7.82 (m, 1H). FAB-MS (Li+ spike): calculated
for $\text{C}_{34}\text{H}_{40}\text{N}_4\text{O}_4\text{S}$ 600; found 607 ($\text{M}+\text{Li}$, 65%).

25 Step B: 4'-[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-
amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-
benzazepin-1-yl]methyl][1,1'-biphenyl]-2-
thioamide, trifluoroacetate

30 A suspension of 80mg (0.13mmol) of the
intermediate prepared in Step A in 10mL of methylene

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chloride at room temperature was treated with 5mL of trifluoroacetic acid. After 45 minutes, all volatiles were removed under vacuum and the residue placed under high vacuum. Purification by preparative thin layer chromatography on a 1mm silica plate eluting with methylene chloride/methanol/acetic acid (9:1:0.1) afforded 43mg of the free amine which was converted to the trifluoroacetate salt by dissolving in 3mL of methanol and adding 0.5mL of trifluoroacetic acid, followed by removal of volatiles under vacuum. In this manner, 30mg (0.05mmol, 37%) of the title compound was obtained.

¹H NMR (400MHz, CD₃OD): 1.35 (s,3H), 1.39 (s,3H), 2.11 (m,1H), 2.31 (m,1H), 2.45-2.65 (m,4H), 4.40 (dd;7,11Hz;1H), 4.94 (d,15Hz,1H), 5.24 (d,15Hz,1H), 7.20-7.55 (m,12H). FAB-MS: calculated for C₂₉H₃₂N₄O₂S 500; found 501 (M+H,100%).

Example 94

20

N-Hydroxy-4'-[[[3(R)-[(3-amino-3-methyl-1-oxobutyl)-amino]2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl]-[1,1'-biphenyl]-2-carboxamide, trifluoroacetate

25

Step A: N-Hydroxy-4'-[[2,3,4,5-Tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxy)carbonyl]amino]butyl]-amino]-2-oxo-1H-1-benzazepin-1-yl]-methyl]-[1,1'-biphenyl]-2-carboxamide

30

Prepared from 4'-[[2,3,4,5-Tetrahydro-3(R)-[[3-methyl-1-oxo-3-[(benzyloxy)carbonyl]amino]butyl]-amino]-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-

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biphenyl]-2-carboxylic acid (Example 72, Step B) and (0-trimethylsilyl)hydroxylamine by the procedure described in Example 72, Step C. ^1H NMR (200MHz, CDCl_3): 1.33 (s, 3H), 1.36 (s, 3H), 1.77 (m, 1H), 2.3-2.5 (m, 4H), 4.46 (m, 1H), 4.68 (d, 15Hz, 1H), 5.02 (s, 2H), 5.14 (d, 15Hz, 1H), 5.73 (br s, 1H), 6.82 (d, 7Hz, 1H), 7.1-7.5 (m, 16H), 7.60 (d, 8Hz, 1H). FAB-MS: calc. for $\text{C}_{37}\text{H}_{38}\text{N}_4\text{O}_6$ 634; found 635 ($\text{M}+\text{H}, 1\%$).

10

Step B: N-Hydroxy-4'--[[3(R)-[(3-amino-3-methyl-1-oxo-butyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide. trifluoroacetate

15

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 79. ^1H NMR (200MHz, CD_3OD): 1.36 (s, 3H), 1.39 (s, 3H), 2.0-2.7 (m, 6H), 4.41 (dd, 7, 11Hz; 1H), 5.03 (d, 15Hz, 1H), 5.18 (d, 15Hz), 7.2-7.6 (m, 12H). FAB-MS: calculated for $\text{C}_{29}\text{H}_{32}\text{N}_4\text{O}_4$ 500; found 502 (100%).

Example 95

25 4'--[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-nitro-1,1'-biphenyl. trifluoroacetate

30

Step A: 4'-Methyl-2-nitro-1,1'-biphenyl

Prepared from 4-methylphenyltrimethylstannane (Example 69, Step A) and 2-bromonitrobenzene by the procedure described in Example 69, Step B.

^1H NMR (200MHz, CDCl_3): 2.39 (s, 3H), 7.23 (m, 3H), 7.45 (m, 3H), 7.58 (t, 7Hz, 1H), 7.80 (d, 7Hz, 1H).

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Step B: 4'-Bromomethyl-2-nitro-1,1'-biphenyl

Prepared from 4'-methyl-2-nitro-1,1'-biphenyl by the procedure described in Example 69,
5 Step C. ^1H NMR (200MHz, CDCl_3): 4.53 (s, 2H), 7.2-7.7 (m, 7H), 7.85 (m, 1H). FAB-MS: calculated for $\text{C}_{14}\text{H}_{10}\text{BrN}$ 272; found 272, 274 (M^+). ^1H NMR indicates the presence of minor amounts of starting material and dibromo derivative.

10

Step C: 3-[[1-[[2'-Nitro-[1,1'-biphenyl]-4-yl]-methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxopropylcarbamic acid. 1,1-dimethylethyl ester

15 Prepared from 4'-bromomethyl-2-nitro-1,1'-biphenyl and 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) by the procedure described in Example 69, Step D. ^1H NMR (200MHz, CDCl_3): 1.34 (s, 6H), 1.41 (s, 9H), 1.83 (m, 1H), 2.35-2.70 (m, 5H), 4.50 (m, 1H), 4.84 (d, 15Hz, 1H), 5.23 (d, 15Hz, 1H), 5.27 (s, 1H), 6.64 (d, 7Hz, 1H), 7.1-7.6 (m, 11H), 7.80 (d, 8Hz, 1H).

20 25 Step D: 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-nitro-1,1'-biphenyl, trifluoroacetate

30 Prepared from the intermediate obtained in Step C by the procedure described in Example 69, Step F. ^1H NMR (400MHz, CD_3OD): 1.34 (s, 3H), 1.38 (s, 3H), 2.11 (m, 1H), 2.32 (m, 1H), 2.4-2.7 (m, 4H), 4.40

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(dd;8,11Hz;1H), 4.99 (d,15Hz,1H), 5.21 (d,15Hz,1H),
7.1-7.4 (m,8H), 7.45 (d,8Hz,1H), 7.54 (t,8Hz,1H),
7.67 (t,8Hz,1H), 7.85 (d,8Hz,1H). FAB-MS:
calculated for C₂₈H₃₀N₄O₄ 486; found 487 (M+H, 90%).

5

Example 96

2-Amino-4'-'-[3(R)-[(3-amino-3-methyl-1-oxobutyl)-
10 amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-
methyl]-1,1'-biphenyl trifluoroacetate

A solution of 200mg (0.34mmol) of the intermediate obtained in Example 95 (Step C) in 3mL of methanol was hydrogenated at room temperature and 40psi over 50mg of 5% palladium on carbon for 90 minutes. The catalyst was removed by filtration through Celite and the filtrate evaporated to dryness under vacuum to afford 189mg (0.34mmol, 100%) of product.

The above intermediate (90mg, 0.16mmol) was dissolved in 5mL of methylene chloride and treated with 0.25mL of trifluoroacetic acid. The mixture was stirred at room temperature for 14 hours then all volatiles removed under vacuum to give 46mg (0.10mmol, 62%) of the title compound. ¹H NMR (400MHz, CD₃OD): 1.38 (s,3H), 1.42 (s,3H), 2.13 (m,1H), 2.32 (m,1H), 2.45-2.70 (m,4H), 4.40 (dd;7,11Hz;1H), 5.00 (d,15Hz,1H), 5.29 (d,15Hz,1H), 7.05-7.45 (m,12H). FAB-MS: calculated for C₂₈H₃₂N₄O₂ 456; found 457 (M+H, 100%).

30

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Example 97

5 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,-
5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-
biphenyl]-2-carboxylic acid-N(2)-formylhydrazide,
trifluoroacetate

10 Step A: 4'-[[3(R)-[(3-t-Butoxycarbonylamino-3-methyl-

15 1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-

20 1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-

25 2-carboxylic acid-N(2)-formylhydrazide

A solution of 100mg (0.17mmol) of 4'-[[3(R)-
[(3-t-butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-
2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-
[1,1'-biphenyl]-2-thioamide (Example 93, Step A) in
6mL of tetrahydrofuran was treated with 0.08mL of
methyl iodide and the resulting solution stirred at
room temperature for 14 hours. The mixture was
evaporated under vacuum to give the product which was
used in the next step without purification.

20 A solution of 40mg (0.68mmol) of formic
hydrazide in 2mL of dry dimethylformamide was added
to the intermediate obtained above and the resulting
solution stirred at room temperature for 14 hours.

25 An additional 80mg (1.4mmol) of formic hydrazide was
added and stirring continued for another 5 hours.
The reaction mixture was added to ethyl acetate and
washed with water (4x). The organic layer was
separated, dried over magnesium sulfate, filtered and
solvents removed under vacuum. Purification by
30 preparative thin layer chromatography on silica,
eluting with methylene chloride/methanol (9:1),
afforded 32mg (0.05mmol, 30%) of product. ¹H NMR

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(200MHz, CDCl₃): 1.30 (s, 6H), 1.37 (s, 9H), 1.84
(m, 1H), 2.3-2.6 (m, 5H), 4.50 (m, 1H), 4.76
(d, 15Hz, 1H), 4.98 (br s, 2H), 5.24 (d, 15Hz, 1H), 5.53
(br s, 1H), 7.1-7.6 (m, 12H), 8.34 (br s, 1H).

5

Step B: 4'-[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-
amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benz-
azepin-1-yl]methyl][1,1'-biphenyl]-2-carboxy-
lic acid-N(2)-formyl hydrazide, trifluoro-
acetate

10

Prepared from the intermediate obtained in
Step A by the procedure described in Example 69, Step
F. ¹H NMR (400MHz, CD₃OD): 1.35 (s, 3H), 1.39
(s, 3H), 2.12 (m, 1H), 2.22 (m, 1H), 2.35-2.70 (m, 4H),
15 4.39 (m, 1H), 4.9 (m, 1H), 5.3 (m, 1H), 7.2-7.8 (m, 12H),
8.20 (s, 1H). FAB-MS: calculated for C₃₀H₃₃N₅O₄
527; found 534 (M+Li, 10%).

Example 98

20

4'-[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,-
5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-
(hydroxyacetyl)-1,1'-biphenyl, trifluoroacetate

25

Step A: 4'-Methyl-2-acetyl-1,1'-biphenyl

Prepared from 4-methylphenyltrimethyl-
stannane (Example 69, Step A) and 2'-bromoacetophe-
none by the procedure described in Example 69, Step
B. ¹H NMR (200MHz, CDCl₃): 1.98 (s, 3H), 2.37
30 (s, 3H), 7.20 (s, 4H), 7.3-7.5 (s, 4H). FAB-MS:
calculated for C₁₅H₁₄O 210; found 211 (M+H, 100%).

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Step B: 4'-Methyl-2-(bromoacetyl)-1,1'-biphenyl

A solution of 4'-methyl-2-acetyl-1,1'-biphenyl (2.06g, 9.79mmol) in 10mL of glacial acetic acid was treated dropwise with a solution of bromine (1.722g, 1.07mmol) dissolved in 3.0mL of glacial acetic acid. After initiating the reaction with the first few drops of the bromine/acetic acid reagent by heating the reaction mixture at 30°C, the remainder of the bromine solution was added dropwise at 25-30°C. The reaction mixture was stirred at room temperature until the consumption of bromine was complete (approximately 2 hrs). The reaction mixture was diluted with 150mL of hexane then washed with water (3x50mL). The organic layer was removed, dried over magnesium sulfate, filtered and evaporated under vacuum to give 2.92g of an oil that was used in the next step without purification. ^1H NMR (crude product) (200MHz; CDCl_3): 2.38 (s, 3H), 3.66 (s, 2H), 7.21 (s, 4H), 7.3-7.6 (m, 4H).

20

Step C: 4'-Methyl-2-(acetoxymethyl)-1,1'-biphenyl

A solution of 1.44g (4.98mmol) of 4'-methyl-2-(bromoacetyl)-1,1'-biphenyl in 3.0mL of polyethyleneglycol-400 was added to a solution of 500mg of potassium acetate in 3.0mL of polyethyleneglycol-400. The suspension was heated at 100°C for 30 minutes, then cooled and diluted with 100mL of water. The resultant mixture was extracted with ether; the combined ether extracts were diluted with an equal volume of hexane and washed with water. The organic layer was separated, dried over magnesium sulfate, filtered, and the solvent was removed under

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vacuum to yield an oil which was purified by silica chromatography, eluting with hexane/ethyl acetate (8:1) to give 444mg (1.66mmol, 33%) of product as an oil. ^1H NMR (200MHz, CDCl_3): 2.06 (s, 3H), 2.39 (s, 3H), 4.46 (s, 2H), 7.23 (s, 4H), 7.3-7.6 (m, 4H).

5

Step D: 4'-Bromomethyl-2-(acetoxyacetyl)-1,1'-biphenyl

Prepared from 4'-methyl-2-(acetoxyacetyl)-1,1'-biphenyl by the procedure described in Example 10 69, Step C. ^1H NMR (200MHz, CDCl_3): 2.01 (s, 3H), 4.49 (s, 4H), 7.15-7.55 (m, 8H).

15
Step E: 3-[[1-[[2'-(acetoxyacetyl)-[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxo-propylcarbamic acid, 1,1-dimethylethyl ester
Prepared from 4'-bromomethyl-2-(acetoxyacetyl)-1,1'-biphenyl and 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) by the 20 procedure described in Example 69, Step D. ^1H NMR (200MHz, CDCl_3): 1.33 (s, 6H), 1.39 (s, 9H), 1.87 (m, 1H), 2.03 (s, 3H), 2.35-2.70 (m, 5H), 4.36 (s, 2H), 4.51 (m, 1H), 4.85 (d, 15Hz, 1H), 5.28 (d, 15Hz, 1H), 6.66 (m, 1H). 25 7.1-7.6 (m, 12H).

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Step F: 4'-[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-(hydroxyacetyl)-1,1'-biphenyl, trifluoroacetate

5

The title compound was prepared from the intermediate obtained in Step E by the procedure described in Example 69, Step F. ^1H NMR (200MHz, CD₃OD): 1.30 (s, 3H), 1.34 (s, 3H), 2.08 (m, 1H), 2.28 (m, 1H), 2.4-2.6 (m, 4H), 4.01 (s, 2H), 10 4.36 (dd; 8, 11Hz; 1H), 4.95 (d, 15Hz, 1H), 5.17 (d, 15Hz, 1H), 7.1-7.5 (m, 12H). FAB-MS (Li⁺ spike): calculated for C₃₀H₃₃N₃O₄ 499; found 500 (M+H, 18%), 506 (M+Li, 100%).

15

Example 99

4'-[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl]-2-hydroxy-1,1'-biphenyl, trifluoroacetate

20

Step A: 4'-Methyl-2-hydroxy-1,1'-biphenyl

A solution of 4.2g (20.0mmol) of 4'-methyl-2-acetyl-1,1'-biphenyl (Example 98, Step A) in methylene chloride, under a nitrogen atmosphere, 25 was treated with 8.98g of 85% m-chloroperbenzoic acid. The resultant suspension was cooled to 0 °C and treated dropwise with 1.54mL of trifluoroacetic acid over a 10 minute period. The reaction mixture was stirred at room temperature for 16 hours. The 30 reaction mixture was diluted with 50mL of methylene chloride and the solution was washed successively with 50mL of 10% sodium sulfite, 50mL of saturated aqueous potassium carbonate and water (3x50mL). The organic layer was removed and dried over magnesium

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sulfate, then evaporated under vacuum to yield 4.1g of an oil. The oil was dissolved in 20mL of methanol and treated with 2.0mL of 5N aqueous sodium hydroxide. The reaction mixture was stirred at room 5 temperature for 1 hour. The pH of the solution was adjusted to 5-6 with acetic acid. After the methanol was removed under vacuum, the residue was taken up in ether, washed with water, dried over magnesium sulfate, filtered and evaporated under vacuum to yield 3.0g of crude product which was purified by preparative high pressure liquid chromatography on silica, eluting with hexane/ethyl acetate (10:1). In this manner, 1.85g (10.0mmol,50%) of the product was obtained as an oil. ^1H NMR (200MHz,CDCl₃): 2.40 (s,3H), 5.22 (br s,1H), 6.96 (m,2H), 7.2-7.4 (m,6H). EI-MS: calculated for C₁₃H₁₂O 184; found 184 (M⁺,100%).

Step B: 4'-Methyl-2-acetoxy-1,1'-biphenyl

20 A solution of 1.0g (5.4mmol) of 4'-methyl-2-hydroxy-1,1'-biphenyl in 2.0mL of pyridine was treated with 2mL of acetic anhydride. The reaction mixture was stirred at room temperature for 5 hours. The solvent was removed under vacuum to yield 1.11g (4.9mmol,90 %) of the product as an oil. ^1H NMR (200MHz,CDCl₃): 2.07 (s,3H), 2.36 (s,3H), 7.07 (dd;3,8Hz;1H), 7.15 (d,8Hz,2H), 7.2-7.4 (m,5H).

Step C: 4'-Bromomethyl-2-acetoxy-1,1'-biphenyl

30 Prepared from 4'-methyl-2-acetoxy-1,1'-biphenyl by the procedure described in Example 69, Step C. ^1H NMR (200MHz,CDCl₃): 2.05 (s,3H), 4.50 (s,2H), 7.08 (m,1H), 7.20-7.45 (m,7H).

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Step D: 3-[[1-[[2'-acetoxy-[1,1'-biphenyl]-4-y1]-
methy1]-2,3,4,5-tetrahydro-2-oxo-1H-benz-
azepin-3(R)-y1]amino]-1,1-dimethyl-3-oxoprop-
ylcarbamic acid, 1,1-dimethylethyl ester

5 Prepared from 4'-bromomethyl-2-acetoxy-1,1'-
biphenyl and 3-t-butoxycarbonylamino-3-methyl-N-
[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-y1]-
butanamide (Example 57, Step A) by the procedure
described in Example 69, Step D. ¹H NMR
10 (200MHz, CDCl₃): 1.38 (s, 6H), 1.45 (s, 9H), 1.85
(m, 1H), 2.02 (s, 3H), 2.35-2.65 (m, 5H), 4.52 (m, 1H),
4.84 (d, 15Hz, 1H), 5.30 (d, 15Hz, 1H), 6.71 (d, 7Hz, 1H),
7.1-7.4 (m, 12H).

15 Step E: 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-
amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benza-
zepin-1-y1]methyl]-2-hydroxy-1,1'-biphenyl,
trifluoroacetate

20 A solution of 468mg (0.78mmol) of the
intermediate obtained in Step D in 25mL of methanol
was treated with 4.0mL of 5N aqueous sodium hydroxide
and the resultant solution stirred at room temperature
for 1 hour. The solvent was removed under
vacuum to yield the crude intermediate which was used
25 without purification.

The intermediate obtained above was treated
as described in Example 69, Step F to afford the
title compound. ¹H NMR (400MHz, CD₃OD): 1.34 (s, 3H),
1.39 (s, 3H), 2.11 (m, 1H), 2.32 (m, 1H), 2.45-2.70
30 (m, 4H), 4.41 (dd; 8, 11Hz; 1H), 4.95 (d, 15Hz, 1H), 5.23
(d, 15Hz, 1H), 6.86 (d, 8Hz, 2H), 7.11 (m, 1H), 7.15-7.25
(m, 5H), 7.35 (m, 2H), 7.45 (d, 8Hz, 2H).

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Example 100

5 4'-[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]2,3,-
4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]- methyl]-
2-(4-aminophenoxy)-1,1'-biphenyl, di(trifluoroacetate)

Step A: 4'-Methyl-2-(4-nitrophenoxy)-1,1'-biphenyl

10 A solution of 450mg (2.44mmol) of 4'-methyl-
2-hydroxy-1-1'-biphenyl (Example 99, Step A) in 7.0mL
of dimethylformamide was treated with 135mg of 60%
sodium hydride (3.3mmol). The reaction mixture was
stirred at room temperature for 30 minutes then
treated with 428mg (3.03mmol) of 1-fluoro-2-nitro-
benzene. The reaction mixture was heated at 100°C
15 for 2 hours. The reaction mixture was cooled, poured
into 100mL of water and the resultant mixture was
extracted with ethyl ether (3x60mL). The combined
extracts were washed with water (4x50mL), dried over
magnesium sulfate, filtered and evaporated under
vacuum. The residue was chromatographed on silica,
20 eluting with hexane/ethyl acetate (10:1) to give
737mg (99%) of the product. ^1H NMR (200MHz, CDCl_3):
2.28 (s, 3H), 6.83 (d, 8Hz, 2H), 7.08 (d, 8Hz, 2H),
7.3-7.5 (m, 6H), 8.05 (d, 8Hz, 2H).

25

Step B: 4'-Bromomethyl-2-(4-nitrophenoxy)-1,1'-
biphenyl

30 Prepared from 4'-methyl-2-(4-nitrophenoxy)-
1,1'-biphenyl by the procedure described in Example
69, Step C. ^1H NMR (200MHz, CDCl_3): 4.43 (s, 2H),
6.83 (d, 8Hz, 2H), 7.09 (d, 8Hz, 1H), 7.3-7.5 (m, 7H),
8.04 (d, 8Hz, 2H).

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Step C: 3-[[1-[2'-(4-nitrophenoxy)-[1,1'-biphenyl]-4-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxo-propylcarbamic acid, 1,1-dimethylethyl ester

5 Prepared from 4'-bromomethyl-2-(4-nitro-phenoxy)-1,1'-biphenyl and 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-(R)-yl]-butanamide (Example 57, Step A) by the procedure described in Example 69, Step D. ¹H NMR (200MHz, CDCl₃): 1.32 (s, 6H), 1.38 (s, 9H), 1.78 (m, 1H), 2.3-2.7 (m, 5H), 4.47 (m, 1H), 4.75 (d, 15Hz, -1H), 5.13 (d, 15Hz, 1H), 6.63 (d, 7Hz, 1H), 6.75 (d, 8Hz, 2H), 7.05-7.50 (m, /11H), 7.97 (s, 1H), 7.98 (d, 8Hz, 2H).

10 Step D: 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-(4-aminophenoxy)-1,1'-biphenyl, di(trifluoroacetate)

15 The intermediate obtained in Step C (140mg, 0.21mmol) was dissolved in 16mL of methanol and hydrogenated at room temperature and 40psi over 20mg of 10% palladium on carbon for 2 hours. The catalyst was removed by filtration through Celite and the filtrate evaporated under vacuum to yield 140mg of crude product which was used in the next step without purification.

20 The crude intermediate obtained above was converted to the title compound by treatment with trifluoroacetic acid according to the procedure described in Example 69, Step F. ¹H NMR (200MHz, CD₃OD): 1.38 (s, 3H), 1.42 (s, 3H), 2.11 (m, 1H), 2.32

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(m, 1H), 2.45-2.65 (m, 4H), 4.41 (dd, 8, 12Hz; 1H), 4.88 (d, 15Hz, 1H), 5.25 (d, 15Hz, 1H), 6.90 (d, 8Hz, 2H), 7.09 (d, 8Hz, 1H), 7.15-7.50 (m, 13H).

5

Example 101

3-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]phenyl-acetamide, trifluoroacetate

10

Step A: 3-(Bromomethyl)phenylacetonitrile

Prepared from 3-(methyl)phenylacetonitrile by the procedure described in Example 69, Step C.

15

^1H NMR (300MHz, CDCl_3): 3.73 (s, 2H), 4.45 (s, 2H), 7.24 (m, 1H), 7.33 (m, 3H).

20

Step B: 3-[[1-[[1-(Cyanomethyl)phenyl-3-yl]methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-y1]amino]-1,1-dimethyl-3-oxopropylcarbamic acid, 1,1-dimethylethyl ester

25

Prepared from 3-(bromomethyl)phenylacetonitrile and 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-y1]-butanamide (Example 57, Step A) by the procedure described in Example 69, Step D.

^1H NMR

30

(400MHz, CDCl_3): 1.33 (s, 3H), 1.34 (s, 3H), 1.40 (s, 9H), 1.83 (m, 1H), 2.4-2.6 (m, 5H), 3.65 (s, 2H), 4.48 (m, 1H), 4.86 (d, 15Hz, 1H), 5.12 (d, 15Hz, 1H), 5.23 (br s, 1H), 6.60 (d, 7Hz, 1H), 7.1-7.3 (m, 8H). FAB-MS: calculated for $\text{C}_{29}\text{H}_{36}\text{N}_4\text{O}_4$ 504; found 505 ($\text{M}+\text{H}, 10\%$).

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Step C: 3-[[3(R)-[(3-t-Butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]phenylacetamide

Prepared from the intermediate obtained in

5 Step B by the procedure described in Example 69, Step E. ^1H NMR (400MHz, CDCl_3): 1.32 (s, 6H), 1.39 (s, 9H),
1.90 (m, 1H), 2.4-2.6 (m, 5H), 3.46 (d, 15Hz, 1H), 3.50
(d, 15Hz, 1H), 4.48 (m, 1H), 4.93 (d, 15Hz, 1H), 5.07
(d, 15Hz, 1H), 5.49 (br s, 1H), 5.93 (br s, 1H), 6.65
10 (d, 7Hz, 1H), 7.05-7.25 (m, 8H). FAB-MS: calculated
for $\text{C}_{29}\text{H}_{38}\text{N}_4\text{O}_4$ 506; found 507 ($\text{M}+\text{H}, 15\%$).

15 Step D: 3-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]phenylacetamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 69, Step F. ^1H NMR (200MHz,
20 CD_3OD): 1.30 (s, 3H), 1.33 (s, 3H), 2.07 (m, 1H), 2.26
(m, 1H), 2.4-2.6 (m, 4H), 3.39 (s, 2H), 4.33
(dd; 8, 11Hz; 1H), 4.90 (d, 15Hz, 1H), 5.11 (d, 15Hz, 1H),
7.08 (d, 8Hz, 1H), 7.1-7.2 (m, 5H), 7.25 (d, 2Hz, 2H).
FAB-MS: calculated for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_3$ 422; found 423
25 ($\text{M}+\text{H}, 100\%$).

Example 102

30 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

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Step A: 3-[(2-(R)-Benzylxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

5

10

15

20

Prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate (Example 1) and (R)-2-benzylloxylpropanal (prepared from ethyl-D-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett. 1985, 26, 1261-1264.) by the procedure described in Example 86, Step A. ¹H NMR (200MHz, CD₃OD): 1.25 (d, 6Hz, 3H), 1.35 (s, 6H), 2.11 (m, 1H), 2.32 (m, 1H), 2.5-2.7 (m, 4H), 2.95 (m, 1H), 3.17 (m, 1H), 3.80 (m, 1H), 4.40 (m, 1H), 4.44 (d, 11Hz, 1H), 4.64 (d, 11Hz, 1H), 4.90 (d, 15Hz, 1H), 5.02 (d, 15Hz, 1H), 6.99 (d, 8Hz, 2H), 7.1-7.7 (m, 15H). FAB-MS: calculated for C₃₉H₄₃N₇O₃ 657; found 658 (M+H, 100%).

25

Step B: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

30

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 86, Step B. ¹H NMR (400MHz, CD₃OD): 1.22 (d, 6Hz, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 2.10 (m, 1H), 2.31 (m, 1H), 2.45-2.70 (m, 4H), 2.81 (dd; 10, 12Hz; 1H), 3.08 (dd; 4, 12Hz; 1H), 3.92 (m, 1H), 4.36 (dd; 7, 11Hz; 1H), 4.93 (d, 15Hz, 1H), 5.17

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(d,15Hz,1H), 7.04 (d,8Hz,2H), 7.19 (d,8Hz,2H),
7.20-7.35 (m,4H), 7.54 (m,2H), 7.65 (m,2H).

FAB-MS: calculated for $C_{32}H_{37}N_7O_3$ 567; found 568
(M+H,45%).

5

Example 103

10 2-[(2(R)-Hydroxypropyl)amino]-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, trifluoroacetate

15 The title compound was prepared from 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide, trifluoroacetate (Example 63) and (R)-2-benzyloxypropanal (prepared from ethyl-D-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett. 1985, 26, 1261-1264.) by the procedures described in Example 20 86. 1H NMR (200MHz, CD₃OD): 1.16 (d,6Hz,3H), 1.55 (s,3H), 1.64 (s,3H), 2.22 (m,2H), 2.49 (m,2H), 2.74 (dd;9,12Hz; 1H), 2.92 (dd;4,12Hz;1H), 3.94 (m,1H), 4.31 (m,1H), 4.88 (d,15Hz,1H), 5.17 (d,15Hz,1H), 6.98 (d,8Hz,2H), 7.16 (d,8Hz,2H), 7.2-7.4 (m,4H), 25 7.45-7.70 (m,4H). FAB-MS: calculated for $C_{31}H_{35}N_7O_3$ 553; found 554 (M+H,45%).

30

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Example 104

5 3-[(2(R)-Acetoxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

10 To a stirred solution of 20mg (0.028mmol) of 3-[(2(R)-hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 102) in 2mL of methylene chloride at room temperature was added 8.8mg of acetic anhydride (3eq.) followed by 13mg (4eq.) of 4-dimethylaminopyridine. The mixture was stirred for one hour then concentrated under vacuum and the residue purified by reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1%aqueous trifluoroacetic acid (70:30) to afford the title compound.

15 20 ¹H NMR (400MHz, CD₃OD): 1.30 (d, 6Hz, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 2.01 (s, 3H), 2.10 (m, 1H), 2.29 (m, 1H), 2.4-2.7 (m, 4H), 3.15 (dd; 9, 13Hz; 1H), 3.25 (dd; 4, 13Hz; 1H), 4.36 (dd; 8, 12Hz; 1H), 4.9 (d, 15Hz, 1H), 5.07 (m, 1H), 5.19 (d, 15Hz, 1H), 7.04 (d, 8Hz, 2H), 7.19 (d, 8Hz, 2H), 7.20-7.35 (m, 4H), 7.54 (m, 2H), 7.65 (m, 2H). FAB-MS: calculated for C₃₄H₃₉N₇O₄ 609; found 610 (M+H, 75%).

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Example 105

5 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-methyltetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-(R)-yl]butanamide, trifluoroacetate

10 Step A: 3-[(2-(R)-Benzyl oxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-methyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

15 Prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-methyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate (Example 16) by the procedure described in Example 86, Step A. ¹H NMR (200MHz, CD₃OD): 1.29 (d, 7Hz, 3H), 1.35 (s, 6H), 2.12 (m, 1H), 2.35 (m, 1H), 2.5-2.7 (m, 4H), 3.00 (dd; 9, 13Hz; 1H), 3.14 (s, 3H), 3.20 (m, 1H), 3.85 (m, 1H), 4.44 (m, 1H), 4.48 (d, 11Hz, 1H), 4.67 (d, 11Hz, 1H), 4.90 (d, 15Hz, 1H), 5.25 (d, 15Hz, 1H), 7.00 (d, 8Hz, 2H), 7.1-7.5 (m, 12H), 7.6 (m, 2H), 7.75 (m, 1H). FAB-MS: calculated for C₄₀H₄₅N₇O₃ 671; found 672 (M+H, 100%).

30

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Step B: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-methyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

5

10

15

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 86, Step B. ^1H NMR (200MHz, CD₃OD): 1.21 (d, 6Hz, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 2.10 (m, 1H), 2.20-2.70 (m, 5H), 2.78 (dd; 10, 12Hz; 1H), 3.09 (dd; 4, 12Hz; 1H), 3.16 (s, 3H), 3.92 (m, 1H), 4.35 (dd; 8, 12Hz; 1H), 4.85 (d, 15Hz, 1H), 5.32 (d, 15Hz, 1H), 7.00 (d, 8Hz, 2H), 7.15-7.35 (m, 6H), 7.55-7.75 (m, 4H). FAB-MS: calculated for C₃₃H₃₉N₇O₃ 581; found 582 (M+H, 100%).

Example 106

3-[(2(R)-Methoxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

25

30

Step A: 2(R)-Methoxypropionaldehyde

To a solution of 1.00g (9.6mmol) of (R)-(+) methyl lactate in 2 mL of methyl iodide was added 4.45g (19.2mmol) of silver (I) oxide and the resulting mixture heated at reflux for 2 hours. The mixture was cooled, filtered and the excess methyl iodide removed under vacuum at 0°C to afford 0.5g of crude methyl [2(R)-methoxy]propionate which was used in the next step without purification.

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To a stirred solution of 0.5g (4.2mmol) of the intermediate obtained above in 5mL of ether at 0°C was added 5.0mL of 1.0M solution of lithium aluminum hydride in ether over 5 minutes. The resulting mixture was treated with 1mL of 1N sodium hydroxide, filtered, dried over magnesium sulfate and concentrated under vacuum at 0°C to give 0.36g of crude 2(R)-methoxypropanol which was used directly in the next step.

To a stirred suspension of 2.7g (12.6mmol) of pyridinium chlorochromate on Celite (1g) in 8mL of methylene chloride was added 0.36g of crude 2(R)-methoxypropanol and the resulting mixture stirred at room temperature for 3 hours. The reaction mixture was filtered, dried over sodium sulfate, filtered and concentrated under vacuum at 0°C to give approximately 0.3g of crude product which was used in the next step without purification.

Step B: 3-[(2(R)-Methoxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1) and 2(R)-methoxypropionaldehyde (Step A) by the procedure described in Example 86, Step A. ¹H NMR (200MHz, CD₃OD): 1.17 (d, 6Hz, 3H), 1.36 (br s, 6H), 2.11 (m, 1H), 2.31 (m, 1H), 2.45-2.65 (m, 4H), 2.87

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(m,1H), 3.14 (m,1H), 3.31 (s,3H), 3.59 (m,1H), 4.37
(dd;7,11Hz;1H), 4.95 (d,15Hz,1H), 5.15 (d,15Hz,1H),
7.03 (d,8Hz,2H), 7.1-7.4 (m,6H), 7.5-7.7 (m,4H).
FAB-MS: calculated for C₃₃H₃₉N₇O₃ 581; found 582.
5 (M+H,100%).

Example 107

10 3-[(2-Hydroxy-2-methylpropyl)amino]-3-methyl-N-[2,-
3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-
[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-
y1]-butanamide, trifluoroacetate

Step A: 2-Benzyl-2-methyl-3-butene

15 To a stirred suspension of 18.6g of 60%
sodium hydride oil dispersion (0.46mol) in 50mL of
dry tetrahydrofuran at 0°C was added 40g (0.46mol) of
2-methyl-3-buten-2-ol over 30 minutes. The resulting
mixture was warmed to room temperature and stirred
20 for 3 hours, then heated at reflux for an additional
30 minutes. The mixture was cooled to 0°C, treated
with 80g (0.46mol) of benzyl bromide, then heated at
reflux for 5 hours. The reaction mixture was cooled,
filtered and concentrated under vacuum. The residue
25 was purified by distillation under reduced pressure
to give 42g (0.24mol, 52%) of product, b.p. 88-89°C
(2mm). ¹H NMR (200MHz, CDCl₃): 1.38 (s,6H), 4.39
(s,2H), 5.20 (m,2H), 5.95 (m,1H), 7.2-7.4 (m,5H).

30

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Step B: 2-Benzylxy-2-methylpropionaldehyde

A mixture of 100mL of water, 300mL of dioxane, 20g (0.11mol) of 2-benzylxy-2-methyl-3-butene and 1g of osmium tetroxide was stirred at room temperature for 30 minutes then 51g (0.22mol) of finely ground sodium periodate was added in portions over 30 minutes. Stirring was continued for 2 hours then the mixture filtered and the filtrate extracted with several portions of ether. The combined extracts were dried over magnesium sulfate, filtered and the filtrate concentrated under vacuum. Distillation afforded 7.3g (0.041mol, 37%) of product, b.p. 85-88°C (2mm).

15 Step C: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

To a solution of 150mg (0.40mmol) of 3-t-butoxycarbonylamo-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) in 2mL of methylene chloride at 0°C was added 2mL of trifluoroacetic acid and the mixture stirred at room temperature for 1 hour. All volatiles were removed under vacuum to give 130mg (0.33mmol, 84%) of the product.

¹H NMR (200MHz, CD₃OD): 1.33 (s, 3H), 1.37 (s, 3H), 2.12 (m, 1H), 2.3-2.6 (m, 3H), 2.6-3.0 (m, 2H), 4.37 (dd; 8, 12Hz; 1H), 7.02 (d, 8Hz, 1H), 7.1-7.3 (m, 3H). FAB-MS: calculated for C₁₅H₂₁N₃O₂ 275; found 276 (M+H, 100%).

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Step D: 3-(2-Benzylxy-2-methylpropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-(R)-yl]butanamide

Prepared from the intermediate obtained in

5 Step C and 2-benzylxy-2-methylpropionaldehyde by the procedure described in Example 86, Step A.

10 ^1H NMR (200MHz, CD₃OD): 1.32 (s,3H), 1.38 (s,9H), 2.10 (m,1H), 2.41 (m,1H), 2.65 (s,2H), 2.7-2.9 (m,2H), 3.09 (s,2H), 4.40 (m,1H), 4.48 (s,2H), 7.0-7.2 (m,4H), 7.2-7.4 (m,5H). FAB-MS: calculated for C₂₆H₃₅N₃O₃ 437; found 438 (M+H,100%).

Step E: 3-[(2-Benzylxy-2-methylpropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

15 To a stirred solution of 145mg (0.332mmol) of the intermediate obtained in Step D in 2mL of dry dimethylformamide at room temperature under nitrogen was added 67mg of 60% sodium hydride oil dispersion (1.67mmol,5eq.). After 30 minutes, a solution of 20 277mg (0.41mmol,1.2eq.) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphen-4-yl)] tetrazole in 2mL of dry dimethylformamide was added and the mixture stirred 25 at room temperature for 1 hour. The reaction mixture was added to 100mL of ethyl acetate and washed with water (2x) and brine. The organic layer was separated, dried over magnesium sulfate, filtered and 30 concentrated under vacuum.

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The residue was dissolved in 5mL of methanol and treated with 5mL of 9N HCl. The mixture was stirred at room temperature for 2 hours then washed with hexanes (5x) to remove triphenylmethanol. The aqueous layer was removed, filtered and evaporated under vacuum; the residue was purified by reverse phase medium pressure liquid chromatography on C8, eluting with methanol/0.1% aqueous trifluoroacetic acid (65:35) to afford 245mg (0.31mmol, 94%) of product.

¹H NMR (200MHz, CD₃OD): 1.32 (s, 3H), 1.38 (s, 9H), 2.10 (m, 1H), 2.31 (m, 1H), 2.4-2.7 (m, 2H), 2.66 (s, H), 4.39 (dd; 7, 11Hz, 1H), 4.50 (s, 2H), 4.94 (d, 15Hz, 1H), 5.16 (d, 15Hz, 1H), 6.99 (d, 8Hz, 2H), 7.05-7.25 (m, 5H), 7.25-7.45 (m, 6H), 7.55-7.70 (m, 4H). FAB-MS: calculated for C₄₀H₄₅N₇O₃ 671; found 672 (M+H, 100%).

Step E: 3-[(2-Hydroxy-2-methylpropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step E by the procedure described in Example 86, Step B.

¹H NMR (200MHz, CD₃OD): 1.29 (s, 6H), 1.36 (s, 3H), 1.40 (s, 3H), 2.1-2.5 (m, 4H), 2.68 (s, 2H), 2.98 (s, 2H), 4.37 (dd; 7, 11Hz, 1H), 4.94 (d, 15Hz, 1H), 5.17 (d, 15Hz, 1H), 7.04 (d, 8Hz, 2H), 7.20 (d, 8Hz, 2H), 7.20-7.35 (m, 4H), 7.5-7.7 (M, 4H). FAB-MS: calculated for C₃₃H₃₉N₇O₃ 581; found 582 (M+H, 70%).

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Example 108

5 3-[(2(S)-Hydroxy-3-methylbutyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, trifluoroacetate

10 Step A: 3-[(2(S)-Benzylxy-3-methylbutyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, trifluoroacetate

15 Prepared from 2(S)-benzylxy-3-methylbutanal (prepared from L-valine by the method of Li, et al; J. Amer. Chem. Soc., 112, 7659 (1990)) and 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, trifluoroacetate (Example 1), by the procedure described in Example 86, Step A.

20 ¹H NMR (200MHz, CD₃OD): 0.92 (d,7Hz, 3H), 0.98 (d,7Hz, 3H) 1.31 (s,3H), 1.38 (s,3H), 2.0-2.6 (m,5H), 2.62 (s,2H), 2.95 (dd;9,12Hz;1H), 3.15 (dd;3,12Hz;1H), 3.55 (m,1H), 4.40 (dd;7,11Hz;1H), 4.52 (d,12Hz,1H), 4.61 (d,12Hz,1H), 4.89 (d,15Hz,1H), 5.18 (d,15Hz,1H), 6.97 (d,8Hz,2H), 7.1-7.7 (m,15H).

25 FAB-MS: calculated for C₄₁H₄₇N₇O₃ 685; found 687 (100%).

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5

Step B: 3-[(2(S)-Hydroxy-3-methylbutyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

Prepared from the intermediate obtained in Step A by the procedure described in Example 86, Step B.

10

^1H NMR (200MHz, CD₃OD): 0.86 (d, 7Hz, 3H), 0.92 (d, 7Hz, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.67 (m, 1H), 2.0-2.6 (m, 4H), 2.64 (s, 2H), 2.82 (dd; 10, 12Hz, 1H), 3.12 (dd; 3, 12Hz; 1H), 3.48 (m, 1H), 4.37 (dd; 8, 12Hz, 1H), 4.9 (d, 15Hz, 1H), 5.19 (d, 15Hz, 1H), 7.04 (d, 8Hz, 2H), 7.15-7.35 (m, 6H), 7.5-7.7 (m, 4H).

15

FAB-MS: calculated for C₃₄H₄₁N₇O₃ 595; found 597 (100%).

Example 109

20

3-[(2(R)-Hydroxy-3-methylbutyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

25

The title compound was prepared from D-valine and 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1), by the procedures described in Example 108.

30

^1H NMR (200MHz, CD₃OD): 0.86 (d, 7Hz, 3H), 0.88 (d, 7Hz, 3H), 1.32 (s, 3H), 1.33 (s, 3H), 1.65 (m, 1H), 2.00-2.66 (m, 6H), 2.78 (dd; 10, 12Hz, 1H), 3.10

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(dd;2,12Hz,1H), 3.45 (m,1H), 4.34 (dd;8,12Hz,1H),
4.90 (d,15Hz,1H), 5.1 (d,15Hz,1H), 7.02 (d,8Hz,2H),
7.1-7.3 (m,6H), 7.45-7.70 (m,4H). FAB-MS:
calculated for C₃₄H₄₁N₇O₃ 595; found 597 (100%).

5

Example 110

10 4'-[3(R)-[(3-Amino-3-methyl-1-oxobutyl)amino]-
2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-
methyl]-2-phenyl-1,1'-biphenyl, trifluoroacetate

Step A: 2-Bromobiphenyl

15 A solution of 8.8mL of isoamyl nitrite in
120mL of benzene at 45°C was treated dropwise over 30
minutes with a solution of 7.5g of 2-bromoaniline in
30mL of benzene. After the addition was complete,
the mixture was heated at reflux for 90 minutes then
cooled and concentrated under vacuum. The product
20 was purified by preparative high pressure liquid
chromatography on silica, eluting with hexanes. ¹H
NMR (200MHz, CDCl₃): 7.23 (m,2H), 7.35 (m,1H), 7.44
(s,5H), 7.70 (d,8Hz,1H).

25 **Step B: 4'-Methyl-2-phenyl-1,1'-biphenyl**

Prepared from 2-bromobiphenyl and 4-methylphenyltrimethylstannane by the procedure described in Example 69, Step B.

¹H NMR (200MHz, CDCl₃): 2.30 (s,3H), 7.06 (s,4H),
30 7.23 (m,5H), 7.44 (s,4H).

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Step C: 4'-Bromomethyl-2-phenyl-1,1'-biphenyl
Prepared from 4'-methyl-2-phenyl-1,1'-biphenyl by the procedure described in Example 69, Step C.

5

Step D: 4'-[[3(R)-[(3-Amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-2-phenyl-1,1'-biphenyl, trifluoroacetate

10 The title compound was prepared from 3-t-butoxycarbonyl amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) and 4'-bromomethyl-2-phenyl-1,1'-biphenyl by the procedures described in Example 69, Steps D and F. ¹H NMR (300MHz, CD₃OD): 1.32 (s,3H), 1.36 (s,3H), 2.0-2.6 (m,6H), 4.37 (dd;8,12Hz;1H), 4.78 (d,15Hz,1H), 5.28 (d,15Hz,1H), 6.95-7.45 (m,17H).

20

Example 111

25

3-[[2-Hydroxy-3-(4-hydroxyphenyl)-propyl]amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

30

Step A: Ethyl 2-hydroxy-3-(4-hydroxyphenyl)-propionate

To a stirred solution of 0.5g (2.74mmol) of D,L 3-(4-hydroxyphenyl) lactic acid hydrate in 10mL of ethanol was added a catalytic amount of concentrated hydrochloric acid. The mixture was heated at reflux for 2 hours then cooled to room

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temperature and concentrated under vacuum. The residue was dissolved in 50mL of ether and washed with saturated aqueous sodium bicarbonate (1x50mL) and brine (1x50mL). The organic layer was removed, dried over magnesium sulfate, filtered and evaporated under vacuum to afford 0.54g (2.57mmol, 94%) of the ethyl ester. ^1H NMR (200MHz, CDCl_3): 1.26 (t, 7Hz, 3H), 2.86 (dd; 7, 14Hz; 1H), 3.03 (dd; 4, 14Hz; 1H), 4.19 (q, 7Hz, 2H), 4.38 (dd; 4, 7Hz; 1H), 5.60 (br s, 1H), 6.66 (d, 8Hz, 2H), 7.03 (d, 8Hz, 2H).

Step B: Ethyl 2-(t-butyldimethylsiloxy)-3-[4-(t-butyldimethylsiloxyphenyl)]propionate

To a stirred solution of 0.57g (7.4mmol) of ethyl 2-hydroxy-3-(4-hydroxyphenyl)propionate in 10mL of methylene chloride at -78°C was added 2mL of 2,6-lutidine (4eq.) followed by 2.52mL of t-butyldimethylsilyl trifluoromethanesulfonate (4eq.). The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was diluted with 50mL of methylene chloride and washed with 10% hydrochloric acid (2x100mL), saturated aqueous sodium bicarbonate and brine. The organic layer was removed, dried over magnesium sulfate, filtered and concentrated under vacuum to give 1.12g of crude product. A 250mg sample was purified by preparative thin layer chromatography on silica, eluting with hexane/ethyl acetate (90:10) to afford 210mg of pure product. ^1H NMR (200MHz, CDCl_3): 0.13 (s, 6H), 0.76 (s, 9H), 0.94 (s, 9H), 2.76 (dd; 10, 14Hz; 1H), 2.97 (dd; 4, 14Hz; 1H), 4.24 (dd; 4, 10Hz; 1H), 6.73 (d, 8Hz, 2H), 7.05 (d, 8Hz, 2H).

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Step C: 2-(t-Butyldimethylsiloxy)-3-[4-(t-butyl-dimethylsiloxyphenyl)]propanal

To a stirred solution of 210mg (0.48mmol) of ethyl 2-(t-butyldimethylsiloxy)-3-[4-(t-butyldimethylsiloxyphenyl)]propionate in 10mL of ether at -78°C was added dropwise over 5 minutes 1mL of 1.0M solution of diisobutylaluminum hydride in hexane (2eq.). The reaction mixture was poured, with rapid stirring, into 50mL of 10% hydrochloric acid. After stirring for 5 minutes, the mixture was extracted with ether (2x30mL) and the combined extracts dried over magnesium sulfate, filtered and concentrated under vacuum to give approximately 200mg of the product which was used immediately and without further purification.

¹H NMR (200MHz, CDCl₃): 0.14 (s, 6H), 0.80 (s, 9H), 0.95 (s, 9H), 2.76 (dd; 10, 14Hz; 1H), 2.90 (dd; 4, 14Hz; 1H), 4.24 (ddd; 2, 4, 10Hz; 1H), 6.73 (d, 8Hz, 2H), 7.02 (d, 8Hz, 2H), 9.61 (d, 2Hz, 1H).

20

Step D: 3-[{(2-Hydroxy-3-(4-hydroxyphenyl)-propyl)-amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate}

The title compound was prepared as a mixture of two diastereomers from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 1) and 2-(t-butyldimethylsiloxy)-3-[4-(t-butyldimethylsiloxyphenyl)]propanal (Step C) by the procedure described in Example 86, Step A.

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¹H NMR (200MHz, CD₃OD): 1.35 (m, 6H), 2.10 (m, 1H), 2.29 (m, 1H), 2.40-2.75 (m, 6H), 2.85 (m, 1H), 3.07 (m, 1H), 3.90 (m, 1H), 4.33 (dd; 8, 12Hz; 1H), 4.9 (m, 1H), 5.1 (m, 1H), 6.67 (d, 8Hz, 2H), 7.02 (m, 4H), 7.15-7.35 (m, 6H), 7.5-7.7 (m, 4H). FAB-MS: calculated for C₃₈H₄₁N₇O₄ 659; found 659 (40%).

Example 112

10 3-[[2(R)-Hydroxy-2-phenylpropyl]amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, trifluoroacetate

15 Step A: 2(R)-Benzylxy-2-phenylacetaldehyde
Prepared from (R)-(-)-mandelic acid by the procedures described in Example 111 (Steps A, C) and Example 107, Step A.

20 ¹H NMR (200MHz, CDCl₃): 4.51 (d, 12Hz, 1H), 4.65 (d, 12Hz, 1H), 4.77 (d, 2Hz, 1H), 7.35 (m, 10H), 9.61 (d, 2Hz, 1H).

25 Step B: 3-[(2(R)-Benzylxy-2-phenylethyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, trifluoroacetate

30 Prepared 2(R)-benzylxy-2-phenyl acetaldehyde and 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, trifluoroacetate (Example 1) by the procedure described in Example 86, Step A. ¹H NMR (200MHz, CD₃OD): 1.35 (s, 6H), 2.12

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(m, 1H), 2.32 (m, 1H), 2.5-2.7 (m, 4H), 3.22 (m, 2H),
4.32 (d, 12Hz, 1H), 4.43 (d, 12Hz, 1H), 4.45 (m, 1H), 4.67
(t, 7Hz, 1H), 4.99 (d, 14Hz, 1H), 5.13 (d, 14Hz, 1H), 7.02
(d, 8Hz, 2H), 7.10-7.45 (m, 16H), 7.5-7.7 (m, 4H).

5 FAB-MS: calculated for C₄₄H₄₅N₇O₃ 719; found 720
(M+H, 35%).

Step C: 3-[[2(R)-Hydroxy-2-phenylpropyl]amino]-
10 3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3(R)-y1]-butan-
amide, trifluoroacetate

15 The title compound was prepared from the
intermediate obtained in Step B by the procedure
described in Example 86, Step B.

1H NMR (400MHz, CD₃OD): 1.38 (s, 3H), 1.39 (s, 3H),
2.10 (m, 1H), 2.3 (m, 1H), 2.4-2.7 (m, 4H), 3.05 (m, 1H),
3.22 (m, 1H), 4.39 (m, 1H), 4.95 (d, 15Hz, 1H), 5.18
(d, 15Hz, 1H), 7.08 (d, 8Hz, 2H), 7.20-7.45 (m, 11H),
20 7.5-7.7 (m, 4H). FAB-MS: calculated for C₃₇H₃₉N₇O₃
629; found 630 (M+H, 85%).

Example 113

25 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-y1]methyl]-
1H-1-benzazepin-3(R)-y1]-butanamide, hydrochloride,
dihydrate

30 Step A: 1-Tetralone oxime
To 4.6L of water at room temperature in a
4-neck 50L flask sitting in a steam bath apparatus

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equipped with an overhead stirrer, a temperature probe and reflux condenser was added 3.72Kg (27.36mol) of sodium acetate with stirring, followed by 1.9Kg of hydroxylamine hydrochloride (27.36mol).

5 To this slurry at room temperature, 12L of ethanol was added followed by 1.994Kg (13.68mol) of 1-tetralone. Additional ethanol (1.7L) was used to rinse off the funnel and added to the reaction mixture. The resulting light orange slurry was

10 heated to 75°C over 40 minutes and maintained at 75-85°C for another 75 minutes. The reaction mixture was cooled with the aid of ice packed around the flask. When the internal temperature reached 32°C, the reaction mixture was pumped over 15 minutes into

15 60L of ice contained in a 200L vessel. The reaction vessel was washed with an additional 2L of water which was added to the 200L vessel. When the ice melted, the mixture was filtered through a filter pad and the wet cake washed with 4L of water. The wet

20 cake was suction dried for 1 hour then transferred to two trays and dried under vacuum at 40°C for 2 days to give 2.094Kg (13.01mol, 95%) of product.

1H NMR (250MHz, CDCl₃): 1.90 (m, 2H), 2.80 (t, 6Hz, 2H), 2.88 (t, 6Hz, 2H), 7.15-7.35 (m, 3H), 7.90 (d, 8Hz, 1H),

25 8.9 (br s, 1H).

Step B: 2,3,4,5-Tetrahydro-1H-1-benzazepin-2-one

To 10L of methanesulfonic acid in a 22L 3-neck flask equipped with an overhead stirrer, a temperature probe, nitrogen inlet and reflux condenser was added 2.6Kg (18.61mol) of phosphorus pentoxide. An additional 1.6L of methanesulfonic

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acid was used to wash all the phosphorus pentoxide into the vessel. The mixture was heated at 90°C for 2.5 hours then cooled to 50°C using an ice bath and treated with 2.00Kg (12.41mol) of 1-tetralone oxime in several portions over 15 minutes. The mixture was heated at 63°C for 10 minutes then slowly heated to 80°C and kept at 80°C for 3 hours. The reaction mixture was pumped into 70L of ice then treated slowly with 11.25L of 50% aqueous sodium hydroxide over 90 minutes at such a rate so as to maintain the temperature below 28°C. The mixture was filtered and 4L of the filtrate was used to rinse the vessel. The wet cake (pink) was washed with 8L of water then suction dried for 45 minutes then transferred to two trays and dried under vacuum at 40°C for 2 days to give 1.9Kg (11.79mol, 95%) of product. ^1H NMR (250MHz, CDCl_3): 2.24 (m, 2H), 2.38 (t, 6Hz, 2H), 2.82 (t, 6Hz, 2H), 7.03 (d, 8Hz, 1H), 7.13 (m, 1H), 7.24 (m, 2H), 8.63 (br s, 1H).

20

Step C: 3-Iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A suspension of 1.8Kg (11.17mol) of 2,3,4,5-tetrahydro-1H-1-benzazepin-2-one in a mixture of 22.33L of methylene chloride and 11.78L (55.83mol) of hexamethyldisilazane was heated at reflux for 10 minutes then cooled to 30°C and treated with 8.503Kg (33.5mol) of iodine in one portion. The mixture was heated at reflux for 2.5 hours then cooled to room temperature. Aqueous sodium sulfite containing 4.926Kg of sodium sulfite in 44L of water was cooled

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to 0°C and into it was poured the reaction mixture in several portions with vigorous stirring while maintaining the temperature below 10°C. The reaction vessel was rinsed with 3L of methylene chloride and the washing transferred to the quenching mixture. Methylene chloride (17L) was added to the quenching mixture and it was stirred vigorously and the layers allowed to separate. The aqueous layer was removed and reextracted with 12L of methylene chloride. The combined organic layers were washed with 11L of water and concentrated under vacuum to a final volume of approximately 5L. The residue was treated with 55L of toluene and concentrated under vacuum to a final volume of 10L. The resulting slurry was removed by filtration and the filter cake washed with an additional 5L of toluene and dried under vacuum at ambient temperature for 24 hours to give 1.842Kg (6.42mol, 57%) of product.

20 ^1H NMR (200MHz, CDCl_3): 2.6-2.8 (m, 3H), 2.93 (m, 1H), 4.64 (t, 8Hz, 1H), 6.97 (d, 8Hz, 1H), 7.10-7.35 (m, 3H), 7.55 (br s, 1H).

Step D: 3(R)-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one. D-tartrate
25 3-Iodo-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (1.79Kg, 6.24mol) was slurried in 6.2L of methanol and the slurry charged into an autoclave. Condensed ammonia (1.55L) was added and the autoclave closed, with stirring, and heated to 100°C over 1 hour. Heating at 100°C was continued for 2 hours then the autoclave was allowed to cool to room

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temperature over 1 hour, during which time the internal pressure was 150-155psi. The reaction mixture was transferred to a polyethylene jug and the autoclave rinsed with 2x8L of methanol. The washings were concentrated under vacuum at 30°C then combined with the reaction mixture and concentrated to near dryness under vacuum at 30°C. The resulting residue was dissolved in 4L of ethyl acetate then concentrated to dryness under vacuum at 30°C.

Sodium chloride (712g) was dissolved in 2L of water and 1.0Kg of sodium carbonate was dissolved in 6L of water. Two liters of the sodium carbonate solution was added to the concentrated residue and the resulting slurry transferred to an extraction flask. Another 2L portion of the sodium carbonate solution was added to the residue flask and the solution transferred to the extraction flask. The remaining sodium carbonate solution was used in the same way. The sodium chloride solution was added to the sodium carbonate/aminolactam emulsion and the resulting mixture stirred for 10 minutes then extracted with four 6L portions of methylene chloride. The combined methylene chloride layers were concentrated to dryness; the residue was treated with 2L of 200 proof ethanol and the resulting slurry concentrated to dryness under vacuum to give 1.171Kg of crude product.

The crude product was slurried in 8L of ethanol and treated with 900g of D-tartaric acid in one portion. Water (7L) was added and the mixture heated to 77°C, then additional ethanol (45L) was added and heating continued. The solution was cooled

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to 43°C and treated with the seed slurry. (The seed slurry was prepared by the route described above starting with 10.50g of crude product and 9.1g of D-tartaric acid.) The solution was aged at room 5 temperature for 48 hours. The slurry formed was removed by filtration and the wet cake washed with 1.8L of ethanol. The resulting filter cake was suction dried with nitrogen bleeding for 20 hours then transferred into a drying tray and dried under 10 vacuum for 24 hours to give 354g (1.085mol, 17.4%) of the product. ^1H NMR (250MHz, CDCl_3): 2.13 (m,1H), 2.51 (m,2H), 2.73 (m,2H), 3.68 (t,6Hz,1H), 3.98 (s,2H), 7.05 (d,8Hz,1H), 7.16 (t,8Hz,1H), 7.30 (m,2H), 7.6 (br s,5H), 10.26 (br s,1H).

15

Step E: 3(R)-Amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

A solution of 229.23g (0.700mol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one, 20 D-tartrate in 4.1L of water was treated with 194g (1.40mol) of potassium carbonate. Subsequent portions of 100g and 135g of potassium carbonate were added until the pH was 10.5. The mixture was extracted with four 4L portions of methylene chloride which were then combined and dried over magnesium 25 sulfate. The aqueous layer was treated with 1.4Kg of sodium chloride and reextracted with four 4L portions of methylene chloride which were then combined and dried over magnesium sulfate. The two 16L batches of extracts were combined, filtered and concentrated to dryness under vacuum to give 115.5g of product which contained 1.6% of an impurity identified as 30 7-iodo-3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one.

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A solution of 107.02g (0.607mol) of the intermediate obtained above in 1.712L of ethanol was hydrogenated at room temperature and 40psi over 4.00g of 10% palladium on carbon for 4 hours. The catalyst was removed by filtration through solkaflok and the filtrate concentrated to dryness under vacuum to give 101.08g (0.574mol, 94.4%) of product.

Step F: N-Chlorosulfonyl-4,4-dimethylazetidin-2-one

To a 3-neck 12L flask equipped with an overhead stirrer, a 250mL addition funnel topped with a nitrogen inlet and a rubber septum to allow a temperature probe and isobutylene needle was charged 450mL of isobutylene. The flask was cooled in a dry ice-acetone bath. Ethyl ether (450mL) was added and the resulting solution at -60°C was treated with 210mL (2.41mol) of chlorosulfonyl isocyanate over 5 minutes at a rate so as to maintain the internal temperature below -50°C. The mixture was stirred at -50°C to -62°C for 30 minutes then allowed to warm slowly to room temperature and treated with 2250mL of ether. The resulting solution was treated with 750mL of 10% aqueous sodium carbonate slowly in 3 portions. The mixture was transferred into a 4L separatory funnel and the aqueous layer removed. The organic layer was washed with 500mL of water, then removed and treated with 750mL of hexane. As crystallization began, additional hexane (250mL) was added and the mixture concentrated under partial vacuum to a final volume of 3100mL. The solid that formed was removed by filtration with the aid of 200mL of hexane for rinsing. After air drying, the

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wet cake was dried under vacuum at 40°C overnight to give 253g (1.28mol, 53%) of product as a pale yellow crystalline solid. Recycling of the mother liquors gave an additional 100g (19%) of product as a white crystalline solid. ^1H NMR (250MHz, CDCl_3): 1.89 (s, 6H), 3.05 (s, 2H).

Step G: 3-Methoxysulfonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

A suspension of 98.31g (0.530mol) of 3(R)-amino-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one in 1600mL of methanol at room temperature was treated with 155mL (1.112mol) of triethylamine. The resulting suspension was cooled to 0°C and treated with a solution of 110.01g (0.557mol) of N-chlorosulfonyl-4,4-dimethylazetidin-2-one in 960mL of methanol over 20 minutes maintaining the internal temperature below 10°C. Additional methanol (100mL) was used to rinse the flask and the rinse was transferred into the reaction vessel. The reaction mixture was warmed to room temperature and stirred for 90 minutes.

The reaction mixture was concentrated under vacuum to a slurry (600mL) which was diluted with 3180mL of ethyl acetate and treated with 1L of saturated aqueous ammonium chloride and 1L of water. The organic layer was separated, washed with 2L of 1:1 saturated aqueous ammonium chloride/water then 2L of brine. The organic layer was removed and concentrated under vacuum to a final volume of 1.6L.

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The resulting slurry was treated with 1.6L of hexane and then aged at room temperature for 2.5 hours. The solid was removed by filtration and the cake washed with 1L of hexane. The material was air dried at 5 40°C for 48 hours to give 163.81g (0.444mol, 83.7%) of product as a white solid.

10 ^1H NMR (250MHz, CDCl_3): 1.39 (s, 3H), 1.42 (s, 3H), 2.04 (m, 1H), 2.37 (d, 15Hz, 1H), 2.58 (d, 15Hz, 1H), 2.69 (m, 2H), 2.95 (m, 1H), 3.81 (s, 3H), 4.55 (m, 1H), 6.83 (m, 2H), 7.01 (d, 8Hz, 1H), 7.25 (m, 3H), 8.20 (br s, 1H).

15 Step H: 3-Methoxysulfonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide

To a suspension of 155.0g (0.4197mol) of the intermediate obtained in Step G in 800mL of tetrahydrofuran was added 140mL of dimethylformamide 20 and the resulting solution cooled to 0° to -5°C and treated with 19.1g of 95% sodium hydride (0.796mol). Additional tetrahydrofuran (40mL) was used to rinse the addition funnel. The mixture was stirred for 30 minutes at 0°C then treated with a solution of 269.0g (0.4825mol) of N-triphenylmethyl-5-[2-(4'-bromomethyl-biphen-4-yl)] in 800mL of tetrahydrofuran over 20 minutes. After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 5 hours. An additional 1.0g of 95% 25 sodium hydride was added and stirring continued for another 3.5 hours.

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The reaction mixture was poured into a mixture of 3L of ethyl acetate and 2.5L of water. Additional water (300mL) and ethyl acetate (500mL) were used for rinsing. The aqueous layer was removed and the organic layer washed with 2L of brine. The 5 organic layer was separated, dried over sodium sulfate, filtered and concentrated under vacuum to a viscous oil. The oil was further concentrated under vacuum to form a pale yellow solid which was purified 10 by chromatography on silica, eluting with ethyl acetate/hexanes (1:1 to 3:1) to afford 330.6g (0.3908mol, 89.3%) of product as a white solid.

Step I: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, mono(hydrochloride), di(hydrate)

To 900mL of hot (70°C) ethanol was added, with vigorous stirring, 190.0g (0.2246mol) of the 15 intermediate obtained in Step H by a solid addition funnel. Additional ethanol (50mL) was used to rinse the funnel. To the clear solution at 70°C was added 380mL of 6N hydrochloric acid over 10 minutes. The 20 mixture was stirred at 70°C for 4.5 hours then allowed to cool to room temperature. The reaction 25 mixture was poured into a mixture of 1900mL of water and 3L of ethyl acetate/hexane (2:1). The aqueous layer was removed and washed with 3L of ethyl acetate/hexane (2:1) then 2.5L of hexane. The 30 aqueous layer was separated and filtered, then concentrated under vacuum at 40°C to a final volume of 3500mL and allowed to age overnight at ambient temperature. The white suspension was removed by

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filtration and the wet cake washed with 250mL of a solution of 15mL of concentrated hydrochloric acid in 500mL of water. The product was dried under vacuum at 35-40°C overnight then allowed to equilibrate in ambient humidity to give 110.25g (0.1894mol, 90.7%) of the title compound as a white powdery solid. ^1H NMR (250MHz, CD₃OD): 1.36 (s,3H), 1.40 (s,3H), 2.12 (m,1H), 2.30 (m,1H), 2.50 (m,2H), 2.55 (m,2H), 4.36 (dd;8,12Hz;1H), 4.87 (d,15Hz,1H), 5.21 (d,15Hz,1H), 7.00 (m,2H), 7.17 (m,2H), 7.22 (m,2H), 7.31 (m,2H), 7.51 (m,1H), 7.53 (m,1H), 7.61 (m,2H).

Example 114

15 3-[(2,2-Dimethyl-1,3-dioxolane-4(S)-yl)methyl]amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide. mono(trifluoroacetate)

To a stirred solution of 116mg (0.20mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride, dihydrate (Example 113) in 5mL of dry methanol was added 0.5g of dry 3A powdered molecular sieves followed by a solution of 131mg (1.0mmol) of D-glyceraldehyde acetonide (used crude as prepared according to the procedure of Hertel, L.W.; Grossman, C. S.; Kroin, J.S. Synth. Comm. 1991, 21, 151-154) in 1mL of dry methanol. The pH of the mixture was carefully adjusted to 6.5 with glacial acetic acid and triethylamine. The reaction was stirred at room temperature for 3 hours at which time 1.0mL (1.0mmol)

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of a 1.0M solution of sodium cyanoborohydride in tetrahydrofuran was added dropwise by syringe. The reaction was stirred overnight then filtered through a pad of Celite. The filtrate was diluted with 50% aqueous trifluoroacetic acid and stirred for 3 hours at room temperature. The solution was concentrated under vacuum and the residue purified by preparative reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient; 60% methanol to 85% methanol over 10 minutes). The title compound was thus obtained in addition to the faster eluting major product 3-(2(S),3-dihydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide. ^1H NMR (200MHz, CD₃OD): 1.35-1.40 (m, 12H), 2.05-2.75 (m, 6H), 3.01 (dd; 8, 12Hz; 1H), 3.26 (dd; 3, 12Hz; 1H), 3.78 (dd; 5, 10Hz; 1H), 4.15 (dd; 6, 8Hz; 1H), 4.36 (m, 2H), 4.85 (d, 15Hz, 1H), 5.15 (d, 15Hz, 1H), 7.03 (d, 8Hz, 2H), 7.2-7.4 (m, 6H), 7.5-7.7 (m, 4H).

Example 115

25 3-(2(S),3-Dihydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide. trifluoroacetate

30 The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride, dihydrate (Example 113) and D-glyceraldehyde acetonide by the procedure described in Example 114.

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10 ¹H NMR (200MHz, CD₃OD): 1.37 (s, 3H), 1.39 (s, 3H),
2.05-2.75 (m, 6H), 2.95 (dd; 8, 11Hz; 1H), 3.19
(dd; 3, 11Hz; 1H), 3.56 (m, 2H), 3.84 (m, 1H), 4.35
5 (dd; 8, 12Hz; 1H), 4.93 (d, 15Hz, 1H), 5.16 (d, 15Hz, 1H),
7.04 (d, 8Hz, 2H), 7.15-7.35 (m, 6H), 7.5-7.7 (m, 4H).
FAB-MS: calculated for C₃₂H₃₇N₇O₄ 583; found 585
(100%).

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Example 116

15 3-(2(S),3(S),4-Trihydroxybutyl)amino-3-methyl-N-[2,3,-
4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butan-
amide, trifluoroacetate

20 The title compound was prepared from
3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride,
dihydrate (Example 113) and 5(S)-t-butyldimethylsilyl-
yloxymethyl-2,2-dimethyl-1,3-dioxolan-4(R)-carboxal-
dehyde (Example 82) by the procedure described in
Example 71. ¹H NMR (400MHz, CD₃OD): 1.36 (s, 3H),
1.40 (s, 3H), 2.09 (m, 1H), 2.30 (m, 1H), 2.46 (m, 1H),
25 2.57 (dd; 7, 11Hz; 1H), 2.64 (s, 2H), 3.13 (m, 2H), 3.59
(br s, 3H), 3.92 (m, 1H), 4.35 (dd; 7, 12Hz; 1H), 4.9
(d, 15Hz, 1H), 5.18 (d, 15Hz, 1H), 7.02 (d, 8Hz, 2H), 7.18
(d, 8Hz, 2H), 7.22 (m, 2H), 7.30 (m, 2H), 7.53 (m, 2H),
7.63 (m, 2H). FAB-MS: calculated for C₃₃H₃₉N₇O₅
30 613; found 614 (100%).

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Example 117

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1-benzyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
5 1H-1-benzazepin-3(R)-yl]butanamide, trifluoroacetate

To a stirred solution of 174mg (0.20mmol) of 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1H-1-benzazepin-3(R)-yl]butanamide, hydrochloride, dihydrate (Example 113) in 3mL of tetrahydrofuran and 1mL of dimethylformamide was added 0.22mL (5eq.) of triethylamine followed by 0.043mL (1.2eq.) of benzyl bromide. The mixture was stirred for 2 hours at room temperature then concentrated under vacuum. Initial purification by reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (75:25) afforded a major product (1-benzyl isomer) followed by a minor product (2-benzyl isomer). Repurification of each product by reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (70:30) afforded 9mg of the title compound in addition to 8mg of the 2-benzyl isomer.

15 ^1H NMR (200MHz, CD₃OD): 1.35 (s,3H), 1.39 (s,3H), 2.05-2.65 (m,6H), 4.38 (dd;7,11Hz,1H), 4.82 (d,15Hz,1H), 4.85 (s,2H), 5.35 (d,15Hz,1H), 6.77 (dd;2,8Hz,2H), 6.94 (d,8Hz,2H), 7.1-7.8 (m,13H).

20 FAB-MS: calculated for C₃₆H₃₇N₇O₂ 599; found 601 (100%).

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Example 118

5 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(2-benzyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

10 The title compound was prepared from
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride,
15 dihydrate (Example 113) and benzyl bromide by the
procedure described in Example 117.

20 ¹H NMR (200MHz, CD₃OD): 1.35 (s, 3H), 1.39 (s, 3H),
2.00-2.65 (m, 6H), 4.40 (dd; 7, 11Hz; 1H), 4.88
15 (d, 15Hz, 1H), 5.26 (d, 15Hz, 1H), 5.74 (s, 2H), 6.96
(d, 8Hz, 2H), 7.10 (d, 8Hz, 2H), 7.25 (m, 3H), 7.30-7.65
(m, 9H), 7.73 (dd; 2, 7Hz; 1H). FAB-MS: calculated for
C₃₆H₃₇N₇O₂ 599; found 601 (100%).

20 Example 119

25 3-(3(R)-Hydroxybutyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

30 The title compound was prepared from
3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride,
dihydrate (Example 113) and 3(R)-hydroxybutanal-0-tetrahydropyranyl ether (prepared from methyl
3(R)-hydroxybutyrate by the method of Sato:
Heterocycles, 24, 2173 (1986)) by the procedure
described in Example 71.

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1H NMR (200MHz, CD₃OD): 1.12 (d, 6Hz, 3H), 1.33 (s, 3H),
1.36 (s, 3H), 1.70 (m, 3H), 2.00-2.60 (m, 5H), 3.09
5 (m, 2H), 3.82 (m, 1H), 4.34 (dd; 7, 11Hz; 1H), 4.85
(d, 15Hz, 1H), 5.18 (d, 15Hz, 1H), 7.00 (d, 8Hz, 2H),
7.1-7.3 (m, 6H), 7.5-7.7 (m, 4H). FAB-MS: calculated
for C₃₃H₃₉N₇O₃ 581; found 583 (100%).

Example 120

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3-(3(S)-Hydroxybutyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,
trifluoroacetate

15

The title compound was prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride, dihydrate (Example 113) and 3(S)-hydroxybutanal-0-tetrahydropyranyl ether (prepared from methyl 3(S)-hydroxybutyrate by the method of Sato: Heterocycles, 24, 2173 (1986)) by the procedure described in Example 71.

25

1H NMR (200MHz, CD₃OD): 1.15 (d, 6Hz, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 1.70 (m, 3H), 1.9-2.6 (m, 5H), 3.10 (m, 2H), 3.84 (m, 1H), 4.33 (dd; 8, 12Hz; 1H), 4.85 (d, 15Hz, 1H), 5.19 (d, 15Hz, 1H), 7.00 (d, 8Hz, 2H), 7.10-7.35 (m, 6H), 7.45-7.70 (m, 4H). FAB-MS:
calculated for C₃₃H₃₉N₇O₃ 581; found 583 (100%).

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Example 121

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[3-bromo-2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, tri-fluoroacetate

Step A: 2-Bromo-4-iodotoluene

A well stirred solution of 18.6g (0.10mol) of 3-bromo-p-toluidine in 80mL of 6N HCl at 0°C was treated with a solution of 7.35g (0.11mol) of sodium nitrite in 15mL of water at a rate that maintained the temperature <10°C. The mixture was stirred for 45 minutes then cautiously treated with 33.2g (0.20mol) of potassium iodide at 0°C. The mixture was treated with 300mL of ether and washed (3x) with saturated aqueous sodium bisulfite. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was redissolved in 50mL of hexane, filtered through 30g of silica and concentrated under vacuum to afford 15.6g (0.053mol, 53%) of the product which was determined to be 65% pure by ¹H NMR. ¹H NMR (200MHz, CDCl₃): 2.33 (s, 3H), 6.97 (d, 8Hz, 1H), 7.51 (dd, 2,8Hz, 1H), 7.86 (d, 2Hz, 1H).

Step B: 2'-(N-Triphenylmethyl)tetrazol-5-yl]-2-bromo-1-methyl-1,1'-biphenyl

A solution of 6.0g (15mmol) of 5-phenyl-2-trityltetrazole (Example 1, Step H) in 60mL of tetrahydrofuran at -15°C to -10°C was treated with 6.5mL of 2.5M n-butyllithium in hexane

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(16.3mmol, 1.05eq) and the resulting mixture stirred for 1.5 hours at -5°C to -10°C then treated with 9.2mL of 1.0M solution of zinc chloride in ether (9.2mmol, 0.6eq). The mixture was warmed to room temperature and treated with: 0.3g of bis(triphenylphosphine) nickel dichloride, 0.3mL of a 3M solution of methylmagnesium chloride in tetrahydrofuran and finally, a solution of 8.5g (29mmol) of 2-bromo-4-iodotoluene in 12mL of tetrahydrofuran. The mixture was stirred overnight at room temperature then treated with an additional 1.5g of 2-bromo-4-iodotoluene and heated briefly to 40°C. The mixture was cooled and partitioned between ether and saturated citric acid. The organic layer was separated, washed with brine (2x), dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was dissolved in methylene chloride, passed through a short plug of silica, and concentrated under vacuum. The gummy residue was dissolved in ether and treated with an equal volume of hexane to precipitate the product. By this method, 4.3g (7.7mmol, 51%) of product was obtained as a white powder. ^1H NMR (400MHz, CDCl_3): 2.29 (s, 3H), 6.83 (t, 8Hz, 2H), 6.89 (d, 8Hz, 6H), 7.2-7.4 (m, 11H), 7.45 (m, 2H), 7.92 (dd; 2, 8Hz; 1H).

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Step C 2'-(N-Triphenylmethyl)tetrazol-5-yl]-2-bromo-1-bromomethyl-1,1'-biphenyl

Prepared from the intermediate obtained in Step B by the procedure described in Example 69, Step C. ^1H NMR (200MHz, CDCl_3): 4.48 (s, 2H), 6.85-7.05 (m, 8H), 7.20-7.55 (m, 13H), 8.03 (m, 1H). ^1H NMR indicates the product thus obtained contains approximately 20% starting material.

10 Step D: 3-t-Butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[3-bromo-2'-(N-triphenylmethyl)tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]-butanamide

15 Prepared from 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) and 2'-(N-triphenylmethyl)tetrazol-5-yl]-2-bromo-1-bromomethyl-1,1'-biphenyl by the procedure described in Example 1, Step K. ^1H NMR (200MHz, CDCl_3): 1.34 (s, 3H), 1.35 (s, 3H), 1.40 (s, 9H), 1.90 (m, 1H), 2.43 (d, 14Hz, 1H), 2.55 (d, 14Hz, 1H), 2.5-2.8 (m, 3H), 4.57 (m, 1H), 4.97 (d, 15Hz, 1H), 5.14 (d, 15Hz, 1H), 5.31 (br s, 1H), 6.66 (d, 7Hz, 1H), 6.95-7.15 (m, 13H), 7.20-7.40 (m, 10H), 7.46 (m, 2H), 7.93 (m, 1H).

25 Step E: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[3-bromo-2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

30 The title compound was prepared from the intermediate obtained in Step D by the procedure described in Example 31, Step H.

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¹H NMR (200MHz, CD₃OD): 1.32 (s, 3H), 1.37 (s, 3H)
2.0-2.9 (m, 6H), 4.40 (dd; 8, 12Hz; 1H), 4.90
(d, 15Hz, 1H), 5.26 (d, 15Hz, 1H), 6.96 (dd; 2, 8Hz, 1H),
5 7.10-7.45 (m, 6H), 7.45-7.70 (m, 4H). FAB-MS:
calculated for C₂₉H₃₀BrN₇O₂ 587,589; found 589
(98%); 591 (100%).

Example 122

10

3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[3-bromo-2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, hydrochloride

15

Step A: 3-[2(R)-Benzylxypropyl]amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

20

Prepared from 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate (Example 107, Step C) and (R)-2-benzylxypropanal (prepared from ethyl-D-lactate according to the procedure of Hanessian and Kloss, Tetrahedron Lett. 1985, 26, 1261-1264.) by the

25

procedure described in Example 86, Step A. ¹H NMR (200MHz, CD₃OD): 1.31 (d, 6Hz, 3H), 1.40 (s, 3H), 1.43 (s, 3H), 2.17 (m, 1H), 2.30 (m, 1H), 2.6-3.1 (m, 5H), 3.22 (dd; 3, 12Hz; 1H), 3.86 (m, 1H), 4.48 (dd; 7, 12Hz; 1H), 4.50 (d, 12Hz, 1H), 4.70 (d, 12Hz, 1H),

30

7.11 (d, 8Hz, 1H), 7.15-7.45 (m, 8H). FAB-MS: calculated for C₂₅H₃₃N₃O₃ 423; found 424 (M+H, 100%).

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Step B: 3-[2(R)-Hydroxypropyl]amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

A solution of 750mg (1.40mmol) of the
5 intermediate obtained in Step A in methanol
containing 2 drops of trifluoroacetic acid was
hydrogenated at room temperature and 40psi in the
presence of 300mg of 30% palladium on carbon for 3
days. The catalyst was removed by filtration through
10 Celite and the filtrate concentrated under vacuum to
give 600mg (1.34mmol, 96%) of product. ^1H NMR
(200MHz, CD_3OD): 1.22 (d, 7Hz, 3H), 1.37 (s, 3H), 1.39
(s, 3H), 2.14 (m, 1H), 2.3-3.0 (m, 6H), 3.09
(dd; 2, 11Hz; 1H), 3.93 (m, 1H), 4.38 (dd; 8, 12Hz; 1H),
15 7.05 (d, 8Hz, 1H), 7.10-7.35 (m, 3H).

Step C: 3-[2(R)-Triethylsiloxypropyl]amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide

20 To a stirred solution of 660mg (1.48mmol) of
the intermediate obtained in Step B in 3mL of
methylene chloride at room temperature was added
1.1mL of N,N-diisopropylethylamine (0.81g, 4.2eq.)
followed by 0.71mL of triethylsilyl trifluoromethane-
25 sulfonate (0.83g, 2.1eq.). The resulting mixture was
stirred at room temperature for 2 hours then
partitioned between ethyl acetate and saturated
aqueous sodium chloride (buffered to pH 9 with 2
drops of ammonium hydroxide). The organic layer was
30 separated, washed with buffered brine, dried over
magnesium sulfate, filtered and solvents evaporated
under vacuum. The residue was purified by

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preparative high pressure liquid chromatography on silica, eluting with ethyl acetate/0.1% ammonium hydroxide in methanol (85:15), to afford 480mg (1.07mmol, 72%) of product. ^1H NMR (200MHz, CD₃OD):
5 0.63 (q, 8Hz, 6H), 0.97 (t, 8Hz, 9H), 1.14 (s, 6H), 1.18 (d, 6Hz, 3H), 2.05 (m, 1H), 2.28 (d, 2Hz, 2H), 2.35-3.00 (m, 5H), 4.01 (m, 1H), 4.44 (dd; 8, 12Hz; 1H), 7.05 (d, 8Hz, 1H), 7.10-7.35 (m, 3H). FAB-MS: calculated for C₂₄H₄₁N₃O₃Si 447; found 448 (M+H, 100%).

10

Step D: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[3-bromo-2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide,
15 hydrochloride

To a stirred solution of 94mg (0.21mmol) of the intermediate obtained in Step C in 0.5mL of dimethylformamide was added 6mg of 60% sodium hydride oil dispersion (3.6mg NaH, 1.2eq.). The resulting solution was stirred for 15 minutes then treated with a solution of 201mg (0.31mmol, 1.5eq.) of 2'-(N-Triphenylmethyl)tetrazol-5-yl]-2-bromo-1-bromo-methyl-1,1'-biphenyl (Example 121, Step C) in 0.5mL of dimethylformamide. The resulting solution was stirred at room temperature for 2 hours then added to 50mL of ethyl acetate and washed with brine (2x). The organic layer was separated, dried over sodium sulfate, filtered and solvents removed under vacuum.

The residue was dissolved in 2mL of methanol and treated with 10mL of 9N HCl and 10mL of hexane. This mixture was stirred vigorously for 2 hours then the layers allowed to separate. The aqueous layer

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was removed by pipet, washed once with hexane, filtered and evaporated under vacuum. The residue was triturated with methanol to give a white solid that was removed by filtration. Thus, 101mg (0.15mmol, 71%) of the title compound was obtained as a white solid. ^1H NMR (300MHz, CD₃OD): 1.23 (d, 6Hz, 3H), 1.40 (s, 3H), 1.41 (s, 3H), 2.24 (m, 1H), 2.40 (m, 1H), 2.61 (d, 15Hz, 1H), 2.69 (d, 15Hz, 1H), 2.7-3.0 (m, 5H), 3.13 (dd; 3, 11Hz; 1H), 3.96 (m, 1H), 4.47 (dd; 7, 12Hz; 1H), 4.9 (d, 15Hz, 1H), 5.38 (d, 15Hz, 1H), 7.17 (d, 8Hz, 2H), 7.25-7.40 (m, 3H), 7.45 (d, 8Hz, 1H), 7.48 (d, 2Hz, 1H), 7.64 (m, 2H), 7.74 (m, 2H). FAB-MS: calculated for C₃₂H₃₆BrN₇O₃ 645,647; found 646(50%), 648(55%).

15

Example 123

3'-Bromo-4'--[[3(R)-[(3-amino-3-methyl-1-oxobutyl) amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl] methyl][1,1'-biphenyl-2-carboxamide, trifluoroacetate

Step A: 3'-Bromo-4'-methyl-1,1'-biphenyl-2-nitrile
A solution of 5.2g (27mmol) of 4'-methyl-1,1'-biphenyl-2-nitrile (Example 69, Step B) in 60mL of methylene chloride at 0°C was treated with 6.7g of silver trifluoroacetate (30mmol). When all the silver trifluoroacetate was dissolved, 1.6mL of bromine was added dropwise (4.95g, 31mmol) with vigorous stirring. After two hours, the reaction mixture was filtered and the solid washed with methylene chloride. The combined organic layers were washed once with dilute (<1N) aqueous sodium

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hydroxide and once with brine. The organic layer was removed, dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was purified by preparative high pressure liquid chromatography on 5 silica, eluting with 10% ether/hexane to give 3g (41%) of product. ^1H NMR (200MHz, CDCl_3): 2.46 (s, 3H), 7.2-7.8 (m, 7H).

10 Step B: 3'-Bromo-4'-bromomethyl-1,1'-biphenyl-2-nitrile

Prepared from the intermediate obtained in Step A by the procedure described in Example 69, Step C. NMR analysis shows product to contain small amounts of starting material and dibromomethyl compound. ^1H NMR (200MHz, CDCl_3): 4.64 (s, 2H), 15 7.4-7.8 (m, 7H). FAB-MS: calculated for $\text{C}_{14}\text{H}_9\text{Br}_2\text{N}$ 351; found 352 (100%); 271 (100%)

20 Step C: 3-[[1-[[3-Bromo-2'-cyano-[1,1'-biphenyl]-4-y1]methyl]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepin-3(R)-yl]amino]-1,1-dimethyl-3-oxo-propylcarbamic acid, 1,1-dimethylethyl ester

Prepared from 3-t-butoxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3(R)-yl]-butanamide (Example 57, Step A) and 3'-bromo-4'-bromomethyl-1,1'-biphenyl-2-nitrile by the procedure described in Example 69, Step D. ^1H NMR (200MHz, CDCl_3): 1.33 (s, 3H), 1.34 (s, 3H), 1.40 (s, 9H), 1.91 (m, 1H), 2.43 (d, 14Hz, 1H), 2.55 (d, 14Hz, 1H), 2.55-2.90 (m, 3H), 4.62 (m, 1H), 4.95 (d, 16Hz, 1H), 5.28 (s, 1H), 5.34 (d, 16Hz, 1H), 6.63 (d, 7Hz, 1H), 7.10-7.25 (m, 4H), 7.45 (m, 4H), 7.64

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(m,1H), 7.75 (m,2H). FAB-MS (Li spike): calculated for C₃₄H₃₇BrN₄O₄ 644, 646; found 651 (13%); 653 (15%).

- 5 Step D: 3'-Bromo-4'--[[3(R)-[(3-t-butoxycarbonylamino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide

The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 69, Step E. ¹H NMR (200MHz,CDCl₃): 1.34 (br s,6H), 1.40 (s,9H), 1.93 (m,1H), 2.43 (d,13Hz,1H), 2.56 (d,13Hz,1H), 2.55-2.90 (m,3H), 4.62 (m,1H), 4.96 (d,16Hz,1H), 5.30 (d,16Hz,1H), 5.34 (br s,1H), 5.65 (br s,1H), 6.69 (d,7Hz,1H), 7.05-7.55 (m,9H), 7.63 (s,1H), 7.71 (dd;2,8Hz;1H). FAB-MS: calculated for C₃₄H₃₉BrN₄O₅ 662, 664; found 663 (2%); 665 (3%).

- 20 Step E: 3'-Bromo-4'--[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step D by the procedure described in Example 69, Step F. ¹H NMR (200MHz,CD₃OD): 1.35 (s,3H), 1.37 (s,3H), 2.10-3.00 (m,6H), 4.48 (dd;8,12Hz;1H), 4.93 (d,16Hz,1H), 5.33 (d,16Hz,1H), 7.15-7.60 (m,10H), 7.67 (d,2Hz,1H). FAB-MS: calculated for C₂₉H₃₁BrN₄O₃ 562, 564; found 563 (38%); 565 (37%).

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Example 124

5 3'-Bromo-4'--[[3(R)-[[3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide. trifluoroacetate

The title compound was prepared from
3'-bromo-4'--[[3(R)-[(3-amino-3-methyl-1-oxo-butyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl][1,1'-biphenyl]-2-carboxamide, trifluoroacetate (Example 123) and D-glyceraldehyde acetonide by the procedure described in Example 71. ¹H NMR (200MHz, CD₃OD): 1.36 (s, 6H), 2.1-3.0 (m, 6H), 3.17 (dd; 4, 12Hz; 1H), 3.50 (m, 2H), 3.83 (m, 1H), 4.46 (dd; 8, 12Hz; 1H), 4.82 (d, 16Hz, 1H), 5.40 (d, 16Hz, 1H), 7.10-7.60 (m, 10H), 7.70 (s, 1H). FAB-MS: calculated for C₃₂H₃₇BrN₄O₅ 636, 638; found 637 (35%); 639 (35%).

20

Example 125

25 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carbomethoxy-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]butanamide. trifluoroacetate

Step A: 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carbomethoxy-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]butanamide

30 Prepared from 3-benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide (Example 51, Step A) and methyl 4'-

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bromomethyl-1,1'-biphenyl-2-carboxylate (prepared by the method of D. J. Carini, et al, EPO publication 324,377) by the procedure described in Example 1, Step K. ^1H NMR (300MHz, CDCl_3): 1.37 (s,3H), 1.39 (s,3H), 1.75 (m,1H), 2.3-2.6 (m,5H), 3.52 (s,3H), 4.50 (m,1H), 4.80 (d,14Hz,1H), 5.06 (s,2H), 5.34 (d,14Hz,1H), 5.65 (s,1H), 6.72 (d,7Hz,1H), 7.1-7.4 (m,15H), 7.48 (dt;2,8Hz;1H), 7.78 (dd;2,8Hz;1H). FAB-MS: calculated for $\text{C}_{38}\text{H}_{39}\text{N}_3\text{O}_6$ 633; found 634 ($\text{M}+\text{H}$, 60%).

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-carbomethoxy-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 1, Step L. ^1H NMR (300MHz, CD_3OD): 1.40 (s,3H), 1.44 (s,3H), 2.17 (m,1H), 2.38 (m,1H), 2.5-2.7 (m,4H), 3.56 (s,3H), 4.46 (dd;8,12Hz;1H), 4.98 (d,15Hz,1H), 5.37 (d,15Hz,1H), 7.22 (d,8Hz,2H), 7.25-7.50 (m,8H), 7.59 (dt;2,8Hz;1H), 7.78 (dd;2,8Hz;1H). FAB-MS: calculated for $\text{C}_{30}\text{H}_{33}\text{N}_3\text{O}_4$ 499; found 500 ($\text{M}+\text{H}$, 100%).

25

Example 126

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-cyano-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

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Step A: 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-cyano-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide
Prepared from 3-benzylloxycarbonylamino-3-

5 methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide (Example 51, Step A) and 4'-bromomethyl-1,1'-biphenyl-2-nitrile (Example 69, Step C) by the procedure described in Example 1, Step K. FAB-MS: calculated for $C_{37}H_{36}N_4O_4$ 600; found 601 ($M+H$, 100%).

10

Step B: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-cyano-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

15

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 1, Step L. 1H NMR (300MHz, CD_3OD): 1.40 (s, 3H), 1.43 (s, 3H), 2.18 (m, 1H), 2.38 (m, 1H), 2.5-2.7 (m, 4H), 4.47 (dd; 8, 12Hz; 1H), 5.11 (d, 15Hz, 1H), 5.28 (d, 15Hz, 1H), 7.30 (m, 2H), 7.35-7.65 (m, 8H), 7.76 (dt; 2, 8Hz; 1H), 7.86 (dd; 2, 8Hz; 1H). FAB-MS: calculated for $C_{29}H_{30}N_4O_2$ 466; found 467 ($M+H$, 100%).

25

Example 127

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-trifluoromethyl-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

30

Step A: 2-Trifluoromethyl-4'-methyl-1,1'-biphenyl

A solution of 388mg (1.52mmol, 1.4eq.) of 4-methylphenyltrimethylstannane (Example 69, Step A)

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in 5mL of toluene under a nitrogen atmosphere was treated with 238mg of 2-bromobenzotrifluoride (1.06mmol) and 64mg of tetrakis(triphenylphosphine) palladium(0) and the resulting solution heated at reflux for 14 hours. The mixture was cooled, filtered and concentrated under vacuum to give an amber oil that was chromatographed on silica, eluting with hexane, to give the product. ^1H NMR (300MHz, CDCl_3): 2.41 (s,3H), 7.2-7.8 (m,8H). EI-MS: calculated for $\text{C}_{14}\text{H}_{11}\text{F}_3$ 236; found 236 (M^+ , 100%).

Step B: 4'-Bromomethyl-2-trifluoromethyl-1,1'-biphenyl
Prepared from 2-trifluoromethyl-4'-methyl-1,1'-biphenyl by the procedure described in Example 15 69, Step C. EI-MS: calculated for $\text{C}_{14}\text{H}_{10}\text{BrF}_3$ 314,316; found 314 (5%),316 (5%).

Step C: 3-Benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-trifluoromethyl-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide
Prepared from 3-benzylloxycarbonylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide (Example 51, Step A) and 4'-bromo-25 methyl-2-trifluoromethyl-1,1'-biphenyl by the procedure described in Example 1, Step K. ^1H NMR (300MHz, CDCl_3): 1.37 (s,3H), 1.39 (s,3H), 1.73 (m,1H), 2.2-2.6 (m,5H), 4.50 (m,1H), 4.82 (d,15Hz,1H), 5.06 (s,2H), 5.29 (d,15Hz,1H), 5.65 (s,1H), 6.70 (d,7Hz,1H), 7.1-7.4 (m,14H), 7.44 (t,8Hz,1H), 7.52 (t,8Hz,1H), 7.71 (d,8Hz,1H). FAB-MS: calculated for $\text{C}_{37}\text{H}_{36}\text{F}_3\text{N}_3\text{O}_4$ 643; found 644 ($\text{M}+\text{H}$, 55%).

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Step D: 3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-trifluoromethyl-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, trifluoroacetate

5 The intermediate obtained in Step C (92mg, 0.14mmol) was treated with 1.62mL of 30% hydrogen bromide in acetic acid at room temperature for 2 hours. The mixture was concentrated under vacuum to give a dark yellow residue. Purification by
10 preparative reverse phase high pressure liquid chromatography on C18, eluting with methanol/0.1% aqueous trifluoroacetic acid (linear gradient: 75% methanol increased to 85% over 10 minutes) afforded 71mg (0.11mmol, 81%) of the title compound as a
15 colorless glass.

1H NMR (300MHz, CD₃OD): 1.39 (s,3H), 1.44 (s,3H), 2.16 (m,1H), 2.38 (m,1H), 2.5-2.7 (m,4H), 4.47 (dd;8,12Hz,1H), 5.04 (d,15Hz,1H), 5.34 (d,15Hz,1H), 7.20-7.45 (m,9H), 7.56 (t,8Hz,1H), 7.66 (t,8Hz,1H),
20 7.79 (d,8Hz,1H). FAB-MS: calculated for C₂₉H₃₁F₃N₃O₂ 509; found 510 (M+H,100%).

Example 128

25 3-Amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

Step A: 6-Methylthio-1-tetralone oxime
30 Prepared from 6-methylthio-1-tetralone (prepared by the method described in EP0 0 325,963 A1) by the procedure described in Example 113, Step A. ¹H

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NMR (200MHz, CDCl₃): 1.89 (m, 2H), 2.52 (s, 3H), 2.78 (m, 4H), 7.02 (d, 2Hz, 1H), 7.08 (dd; 2, 8Hz; 1H), 7.81 (d, 8Hz, 1H).

5 Step B: 7-Methylthio-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Prepared from 6-methylthio-1-tetralone oxime by the procedure described in Example 113, Step B. ¹H NMR (200MHz, CDCl₃): 2.23 (m, 2H), 2.36 (m, 2H), 2.49 (s, 3H), 2.78 (t, 8Hz, 2H), 6.94 (d, 8Hz, 1H), 7.14 (m, 2H), 7.75 (br s, 1H).

10 Step C: 3-Iodo-7-methylthio-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

15 Prepared from 7-methylthio-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the procedure described in Example 31, Step B. ¹H NMR (200MHz, CDCl₃): 2.51 (s, 3H), 2.6-2.9 (m, 3H), 2.50 (s, 3H), 2.97 (m, 1H), 4.68 (t, 9Hz, 1H), 6.95 (d, 8Hz, 1H), 7.15 (m, 2H), 7.5 (br s, 1H).

20 Step D: 3-Amino-7-methylthio-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

25 A mixture of 0.5g of 3-iodo-7-methylthio-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one and 15g of ammonia in 20mL of chloroform was shaken in a bomb at 100°C for 3 hours. The bomb was cooled, vented and the contents transferred to a separatory funnel. The mixture was washed with water, dried over magnesium sulfate, filtered and solvents removed under vacuum to give the product.

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¹H NMR (200MHz, CDCl₃): 1.90 (m, 1H), 2.3-2.7 (m, 2H),
2.45 (s, 3H), 2.85 (m, 1H), 3.39 (dd; 8, 11Hz; 1H), 6.89
(d, 8Hz, 1H), 7.10 (m, 2H), 8.3 (br s, 1H).

5

Step E: 3-t-Butoxycarbonylamino-3-methyl-N-[7-methyl-thio-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-3-yl]-butanamide

Prepared from the intermediate obtained in
10 Step D and 3-t-butoxycarbonylamino-3-methyl-butanoic acid (Example 31, Step E) by the procedure described in Example 1, Step F. ¹H NMR (200MHz, CDCl₃): 1.33 (s, 6H), 1.40 (s, 9H), 1.91 (m, 1H), 2.4-3.0 (m, 5H), 2.48 (s, 3H), 4.50 (m, 1H), 5.22 (br s, 1H), 6.68 (d, 7Hz, 1H),
15 6.90 (d, 8Hz, 1H), 7.11 (m, 2H), 7.66 (br s, 1H).

20 Step F: 3-t-Butoxycarbonylamino-3-methyl-N-[7-methyl-thio-2,3,4,5-tetrahydro-2-oxo-1-[2'-(N-tri phenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3-yl]-butanamide
Prepared from the intermediate obtained in Step E by the procedure described in Example 1, Step K. ¹H NMR (200MHz, CDCl₃): 1.37 (s, 6H), 1.43 (s, 9H),
1.78 (m, 1H), 2.2-2.7 (m, 5H), 2.44 (s, 3H), 4.49 (m, 1H),
25 4.69 (d, 15Hz, 1H), 5.12 (d, 15Hz, 1H), 5.34 (br s, 1H),
6.69 (d, 7Hz, 1H), 6.9-7.1 (m, 12H), 7.2-7.5 (m, 13H),
7.87 (m, 1H).

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Step G: 3-Amino-3-methyl-N-[7-methylthio-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

5 The title compound was prepared from the intermediate obtained in Step F by the procedure described in Example 34, Step K. ¹H NMR (200MHz,DMSO-d₆): 1.24 (s,3H), 1.25 (s,3H), 2.0-2.6 (m,6H), 2.47 (s,3H), 4.25 (m,1H), 4.78 (d,15Hz,1H),
10 5.15 (d,15Hz,1H), 6.97 (d,8Hz,2H), 7.05-7.30 (m,5H), 7.45-7.70 (m,4H), 7.92 (br s,2H), 8.68 (d,7Hz,1H).

Example 129

15 3-Amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide, hydrochloride

20 Step A: 3-t-Butoxycarbonylamino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(N-triphenylmethyl)-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]-butanamide

25 Prepared as a mixture of two racemic diastereomers from the intermediate obtained in Example 128, Step F by the procedure described in Example 48, Step A. ¹H NMR (200MHz,CDCl₃): 1.37 (s,6H), 1.44 (s,9H), 1.90 (m,1H), 2.4-2.9 (m,5H), 2.78 (s,3H), 4.54 (m,1H), 4.76 (two doublets,15Hz,total of 1H), 5.18 (two doublets,15Hz,total of 1H), 5.32 (br s,1H), 6.9-7.1 (m,9H), 7.2-7.6 (m,15H), 7.90 (m,1H), 7.98 (d,8Hz,1H), 8.08 (br s,1H).

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Step B: 3-Amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3-yl]butanamide, hydrochloride

5 The title compound was prepared as a mixture of two racemic diastereomers from the intermediate obtained in Step A by the procedure described in Example 34, Step K.

10 ^1H NMR (200MHz, DMSO-d₆): 1.24 (s, 3H), 1.26 (s, 3H), 2.0-2.8 (m, 6H), 2.78 (s, 3H), 4.25 (m, 1H), 4.94 (d, 15Hz, 1H), 5.19 (d, 15Hz, 1H), 7.01 (d, 8Hz, 2H), 7.16 (d, 8Hz, 2H), 7.5-7.7 (m, 7H), 7.95 (br s, 2H), 8.75 (d, 7Hz, 1H).

15

Example 130

20 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide, trifluoroacetate

25 Step A: 3-Methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]but-2-eneamide
To a suspension of 1.18g (2.64mmol) of 3(R)-amino-1,3,4,5-tetrahydro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-2H-1-benzazepin-2-one, hydrochloride (Example 4, Step C) in 30mL of methylene chloride under nitrogen at -15°C was added 0.923mL (2.64mmol) of triethylamine followed by 0.294mL (2.64mmol) of 3,3-dimethylacryloyl chloride. The reaction mixture was stirred at -15°C for 2 hours then

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quenched by the addition of 1N hydrochloric acid. The mixture was diluted with 50mL of methylene chloride and washed with 50mL of 1N hydrochloric acid and brine. The organic layer was removed and concentrated to dryness under vacuum. The residue was redissolved in 30mL of methanol and treated with 1.5mL of 9N hydrochloric acid. After stirring for 30 minutes, the mixture was concentrated to dryness under vacuum to give 1.3g (2.63mmol, 99%) of the product as a white solid.

¹H NMR (400MHz, CD₃OD): 1.85 (s, 3H), 2.06 (s, 3H), 2.08 (m, 1H), 2.29 (m, 1H), 2.44 (m, 1H), 2.55 (m, 1H), 4.40 (dd; 7, 11Hz; 1H), 4.85 (d, 15Hz, 1H), 5.26 (d, 15Hz, 1H), 5.77 (s, 1H), 7.00 (d, 8Hz, 2H), 7.18 (d, 8Hz, 2H), 7.2-7.4 (m, 4H), 7.54 (m, 2H), 7.64 (m, 2H).

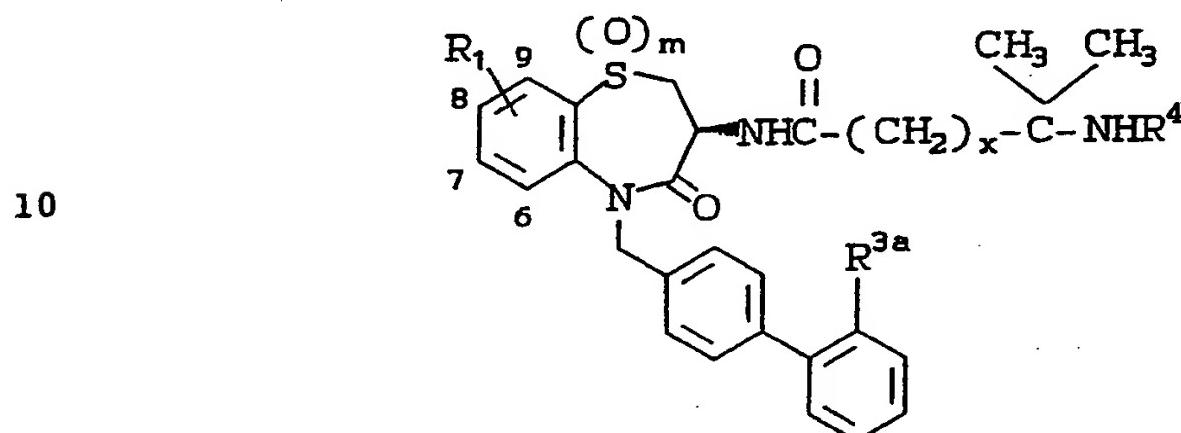
Step B: 3-[(2(R)-Hydroxypropyl)amino]-3-methyl-N-[2, 3, 4, 5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-y1)[1, 1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide, trifluoroacetate

The intermediate obtained in Step A (18mg, 0.037mmol) was dissolved in 2mL of (R)-(-)-1-amino-2-propanol and the resulting solution heated under nitrogen at 120°C for 5 hours. The reaction mixture was cooled, concentrated under vacuum at 50°C and the residue purified by medium pressure liquid chromatography on C8, eluting with methanol/0.1% aqueous trifluoroacetic acid (50:50), to give 14mg (0.021mmol, 57%) of the title compound as a colorless glass. The material thus obtained was identical by 400MHz NMR (CD₃OD), FAB-MS and reverse phase analytical high pressure liquid chromatography to the material obtained in Example 102.

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Example A

Utilizing the general procedures described
in Example 1 to 130, the following compounds of
Formula I can be prepared from the appropriately
5 substituted starting materials and reagents.



	<u>R₁</u>	<u>R^{3a}</u>	<u>R⁴</u>	<u>x</u>	<u>m</u>
15	H			1	0
20	H			1	0
25	H			1	0
30	H		H	0	0
	H			1	1

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Example A (Cont'd)

5

	R_1	R^{3a}	R^4	x	m
10	H		$\begin{array}{c} \text{OH} \\ \\ -\text{CH}_2\text{CHCH}_3 \end{array}$	1	1
15	H		$\begin{array}{c} -\text{CH}_2\text{CH}_2\text{CHCH}_3 \\ \\ \text{OH} \end{array}$	1	1
20	H		$\begin{array}{c} \text{OCH}_3 \\ \\ -\text{CH}_2\text{CHCH}_3 \end{array}$	1	0
25	8-F		$\begin{array}{c} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{array}$	1	0
30	8-CF ₃		$\begin{array}{c} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{array}$	1	0

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Example A (Cont'd)

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	R_1	R^{3a}	R^4	x	m
10	9-F		$-\text{CH}_2\overset{\text{OH}}{\underset{\equiv}{\text{C}}} \text{HCH}_3$	1	0
15	8-OCH ₃		$-\text{CH}_2\overset{\text{OH}}{\underset{\equiv}{\text{C}}} \text{HCH}_3$	1	0
20	8-SCH ₃		$-\text{CH}_2\overset{\text{OH}}{\underset{\equiv}{\text{C}}} \text{HCH}_3$	1	0
	H	$-\text{CO}_2\text{NH}_2$	H	1	0
25	H	$-\text{CO}_2\text{NH}_2$	H	1	1
	H	$-\text{CO}_2\text{NH}_2$	$-\text{CH}_2\overset{\text{OH}}{\underset{\equiv}{\text{C}}} \text{HCH}_3$	1	0

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Example A (Cont'd)

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	R_1	R^{3a}	R^4	x	m
10			$\begin{matrix} OH \\ \equiv \end{matrix}$		
	H	$-CO_2NH_2$	$-CH_2CHCH_2OH$	1	0
15			H	1	0
	H	$-CO_2NHET$	$\begin{matrix} OH \\ \equiv \end{matrix}$		
20			$-CH_2CHCH_3$	1	0
	H	$-CO_2NHET$	$-CH_2CHCH_2OH$	1	0
25			$\begin{matrix} OH \\ \equiv \end{matrix}$		
	H	$-CH_2CONH_2$	$-CH_2CHCH_3$	1	0
30			$\begin{matrix} OH \\ \equiv \end{matrix}$		
	H	$-CH_2CONHET$	$-CH_2CHCH_2OH$	1	0

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Example A (Cont'd)

	R ₁	R ^{3a}	R ⁴	x	m
5	H		H	1	0
10	H		-CH ₂ CH(OH)CH ₃	1	0
15	H		H	1	0
20	H		H	1	0
25	H		H	1	0
30					

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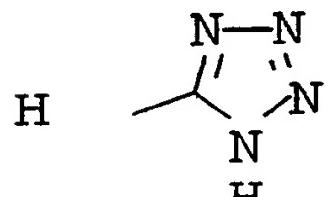
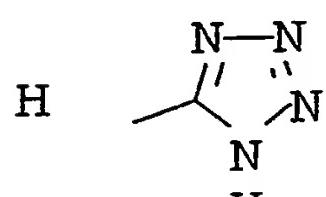
Example A (Cont'd)

	R ₁	R ^{3a}	R ⁴	x	m
5	H		-CH ₂ CH(OH)CH ₂ OH	1	0
10	H	-CONH ₂	H	O	O
	H	-CONHET	H	O	O
15	H	-CH ₂ OH	H	1	0
20	H	-CH ₂ OH	-CH ₂ CH(OH)CH ₃	1	0
	H	-CH ₂ OH	-CH ₂ CH(OH)CH ₃	1	1
25	H	-CH ₂ OH	-CH ₂ CH(OH)CH ₂ OH	1	0
	H	-CH ₂ NH ₂	-CH ₂ CH(OH)CH ₃	1	0
30	H	-CH ₂ NHCOCH ₃	H	1	0

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Example A (Cont'd)

5

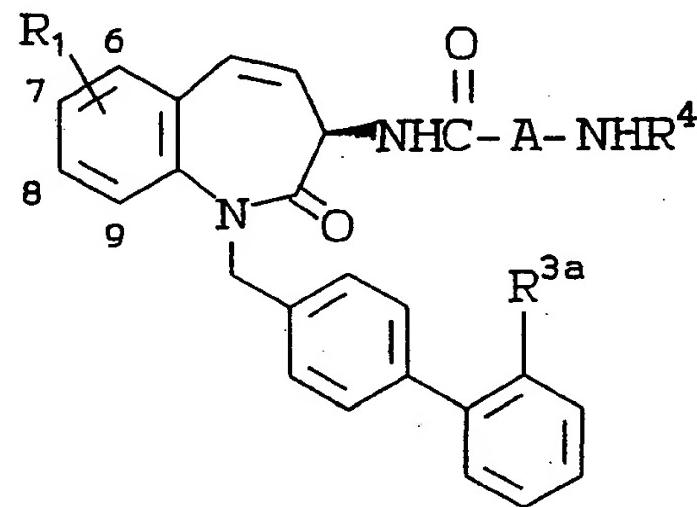
	R_1	R^{3a}	R^4	x	m
10	H	$-CH_2NHCOPh$	H $\equiv OH$	1	0
	H	$-CH_2NHCOCH_3$	$-CH_2CHCH_3$	1	0
15			$\equiv OH$		
	H	$-CH_2NHCOCH_3$	$-CH_2CHCH_2OH$	1	0
20	H		$-CH_2C(CH_3)_2$ $ $ OH	1	0
	H		$-CH_2C(CH_3)_2$ $ $ OH	1	1
25	H	$-CONHOH$	$-CH_2CHCH_3$ $\equiv OH$	1	0
30					

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Example B

Utilizing the general procedures described
in Example 1 to 130, the following compounds of
Formula I can be prepared from the appropriately
5 substituted starting materials and reagents.

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Example B (Cont'd)

	R_1	R^{3a}	R^4	A
5	H		H	
10	H		H	
15	H		$\begin{matrix} \text{OH} \\ \parallel \\ -\text{CH}_2\text{CHCH}_3 \end{matrix}$	
20	H		$\begin{matrix} \text{OH} \\ \downarrow \\ -\text{CH}_2\text{CHCH}_3 \end{matrix}$	
25	H		$-\text{CH}_2\text{CH}_2\text{CHCH}_3$ OH	
30				

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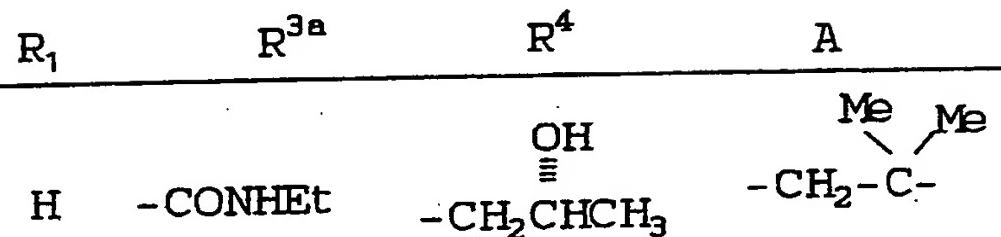
Example B (Cont'd)

	R ₁	R ^{3a}	R ⁴	A
5				
	7-F		-CH ₂ CH(OH)CH ₃	-CH ₂ -C(Me) ₂ -
10				
	7-SCH ₃		-CH ₂ CH(OH)CH ₃	-CH ₂ -C(Me) ₂ -
15				
	7-S(=O)CH ₃		-CH ₂ CH(OH)CH ₃	-CH ₂ -C(Me) ₂ -
20				
	7-OCH ₃		-CH ₂ CH(OH)CH ₃	-CH ₂ -C(Me) ₂ -
25				
	H	-CONH ₂	H	-CH ₂ -C(Me) ₂ -
	H	-CONH ₂	-CH ₂ CH(OH)CH ₃	-CH ₂ -C(Me) ₂ -
30				
	H	-CONHMe	-CH ₂ CH(OH)CH ₃	-CH ₂ -C(Me) ₂ -

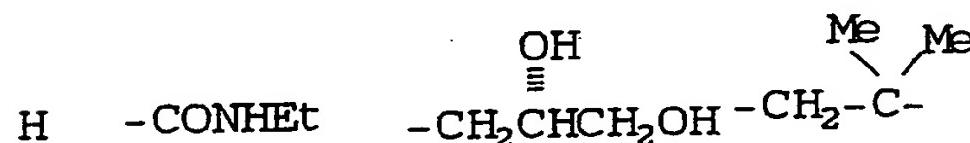
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Example B (Cont'd)

5



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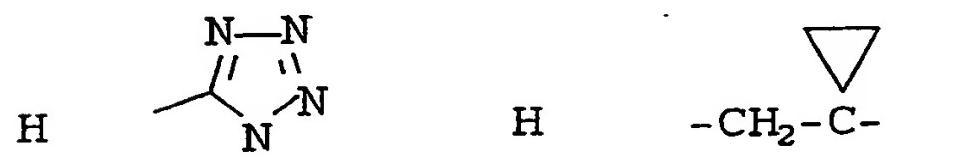
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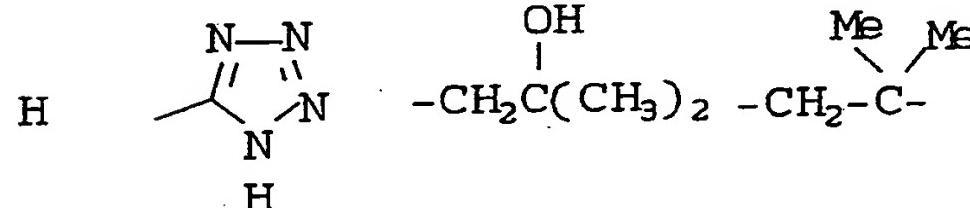
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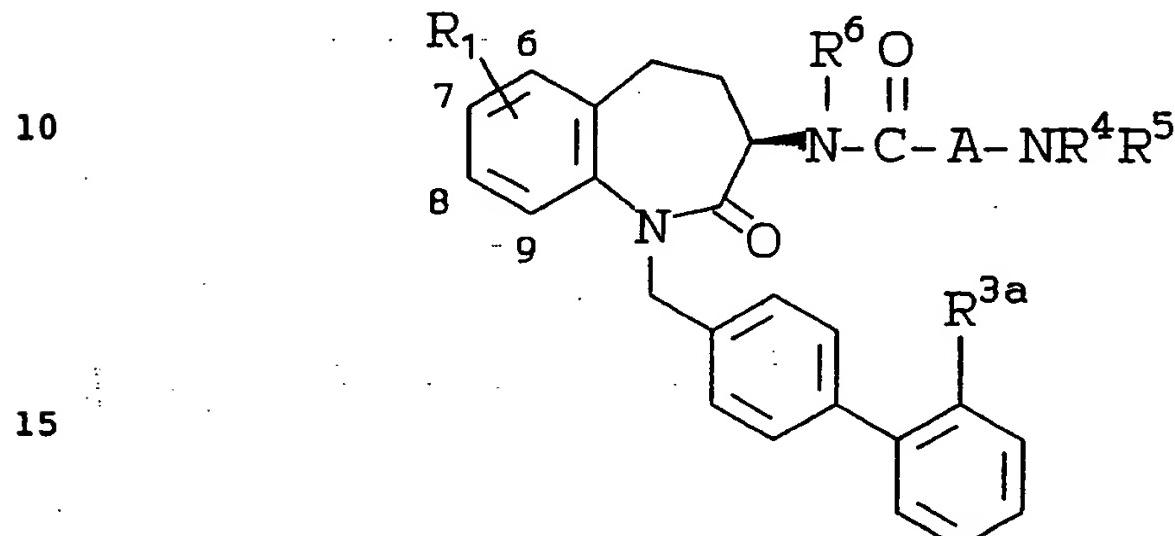
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Example C

Utilizing the general procedures described
in Example 1 to 130, the following compounds of
5 Formula I can be prepared from the appropriately
substituted starting materials and reagents.



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Example C (Cont'd)

5

	R ₁	R ^{3a}	A	R ⁴	R ⁵	R ⁶
7-F	H			H	H	CH ₃
10				H	CH ₃	
15	H			H	H	H
20	H			H	H	H
25	H					
30						

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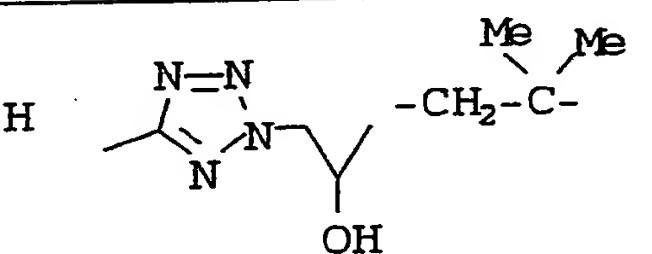
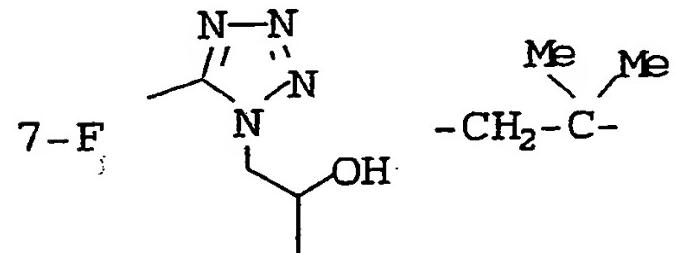
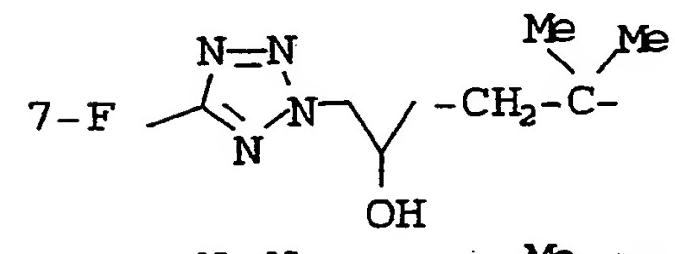
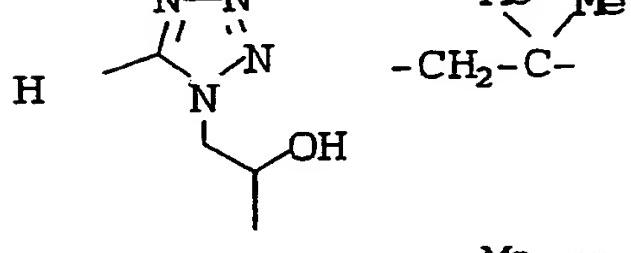
Example C (Cont'd)

5

	R_1	R^{3a}	A	R^4	R^5	R^6
10	H			H	H	H
15	H			H	H	H
20	H				H	H
25	H				H	H
	H				H	H
30	H				H	H

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Example C (Cont'd)

5	R_1	R^{3a}	A	R^4	R^5	R^6
10	H		$-CH_2-C(Me)_2-$	$-CH_2CHCH_3$	H	H
15	7-F		$-CH_2-C(Me)_2-$	H	H	H
20	7-F		$-CH_2-C(Me)_2-$	H	H	H
25	H		$-CH_2-C(Me)_2-$	$-CH_2CH_2OH$	H	H
30	H		$-C(Me)CH_2OH$	H	H	H

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Example C (Cont'd)

5

	R_1	R^{3a}	A	R^4	R^5	R^6
10	H		$-CH_2-C-$ 	H	H	H
15	H		$-CH_2-C-$ 	H	CH_3	H
20	H		$-CH_2-C-$ 	$-CH_2C(CH_3)_2$ 	H	H
25	H	$-CONH_2$	$-CH_2-C-$ 	$-CH_2C(CH_3)_2$ 	H	H
	H	$-CONHET$	$-CH_2-C-$ 	$-CH_2C(CH_3)_2$ 	H	H
30	$7-OCH_3$		$-CH_2-C-$ 	H	H	H

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Example C (Cont'd)

	R ₁	R ^{3a}	A	R ⁴	R ⁵	R ⁶
5						
10	7-OH		-CH ₂ -C(Me) ₂ -	H	H	H
15	7-OCH ₃		-CH ₂ -C(Me) ₂ -	-CH ₂ C(OH)(CH ₃) ₂	H	H
20	7-OH		-CH ₂ -C(Me) ₂ -	-CH ₂ C(OH)(CH ₃) ₂	H	H
25	H		-CH ₂ -C(Me) ₂ -	-CH ₂ C(OH)(CH ₃) ₂	H	H
30	H		-CH ₂ -C(Me) ₂ -	-CH ₂ CH ₂ OCH ₂ CH ₂ -	H	

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Example C (Cont'd)

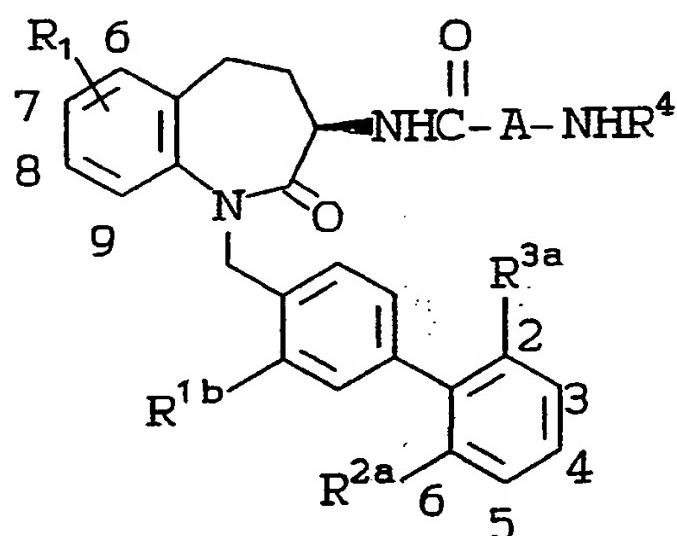
5	R ₁	R ^{3a}	A	R ⁴	R ⁵	R ⁶
10	H	-CONHCH ₃		-CH ₂ CH(Me) ₂	H	H
15	H	-CONHET		CH ₂ CH ₂ CH(Me) ₂	H	H
20	H	-CONHOH		CH ₂ CH ₂ CH(Me) ₂	H	H
25	H	-CONHOH		CH ₂ CH ₂ CH(Me) ₂	H	H
30	H	-CONHOH		-CH ₂ CH ₂ CH(Me) ₂	H	H
	7 - F	-CONHOH		-CH ₂ CH(Me) ₂	H	H

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EXAMPLE D

Utilizing the general procedures described in
Example 1 to 130, the following compounds of Formula
5 I can be prepared from the appropriately substituted
starting materials and reagents.

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Example D (Cont'd)

5

	10 R ₁	R ^{1b}	R ^{2a}	R ^{3a}	A	R ⁴
	H	H		H		H
15	H	H		H		H
20	H	H		H		
25	H	H		H		
30						

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EXAMPLE D (Cont'd)

5

	R_1	R^{1b}	R^{2a}	R^{3a}	A	R^4
10	H	Br	H			H
15	H	Br	H			
20	H	H	H			H
25	H	H	H			
30	H	H	H			

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EXAMPLE D (Cont'd)

5

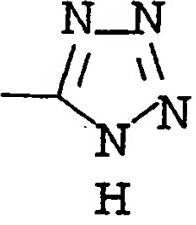
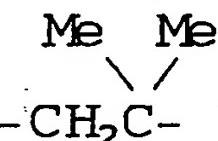
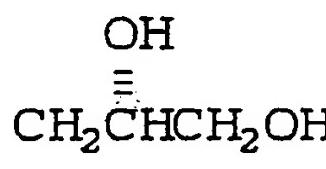
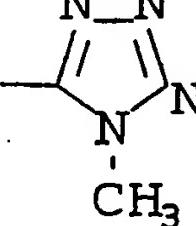
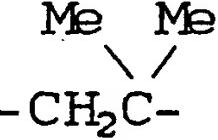
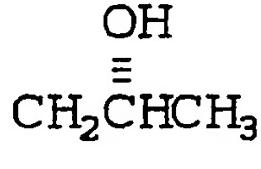
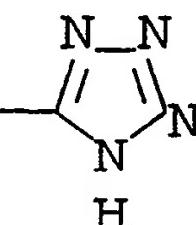
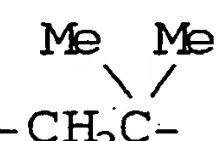
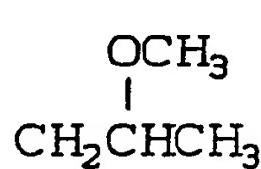
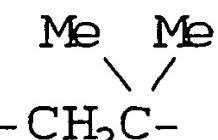
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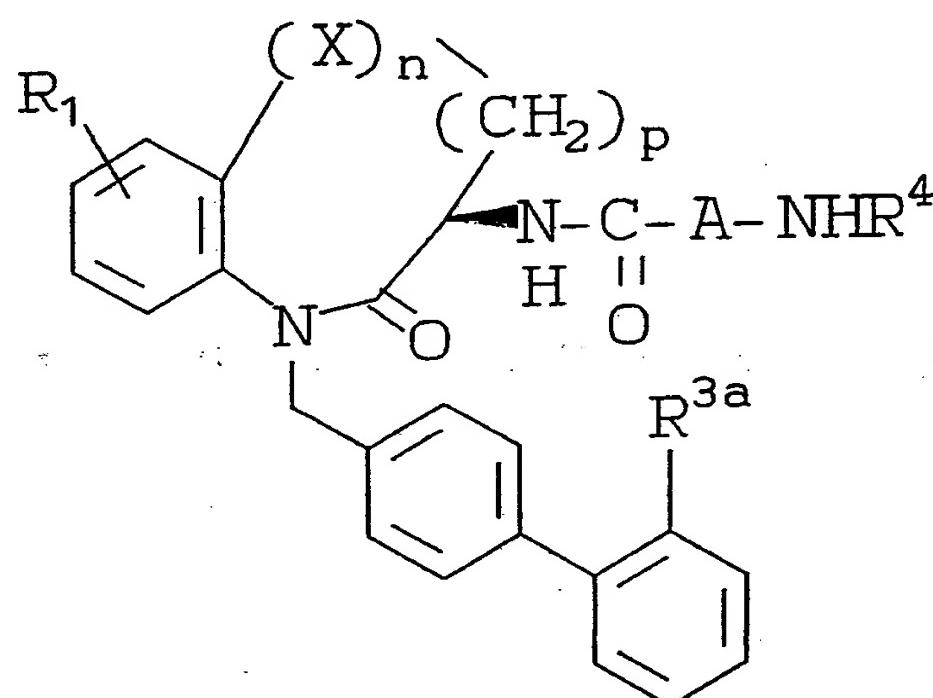
	R_1	R^{1b}	R^{2a}	R^{3a}	A	R^4
	H	H	H			
	H	H	H			
	H	H	H			
	H	Br	H	$-CONH_2$		H

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EXAMPLE E

Utilizing the general procedures described
in Example 1 to 130, the following compounds of
5 Formula I can be prepared from the appropriately
substituted starting materials and reagents.

10



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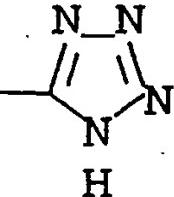
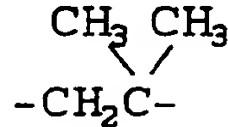
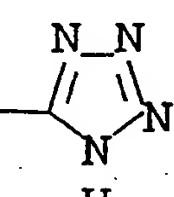
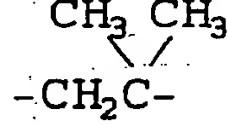
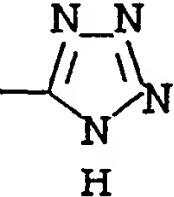
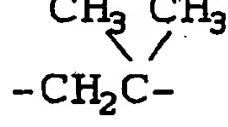
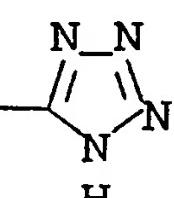
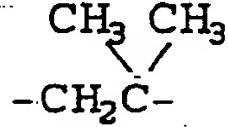
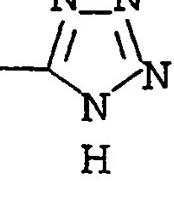
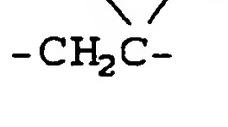
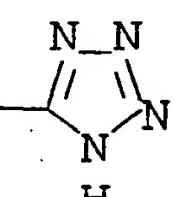
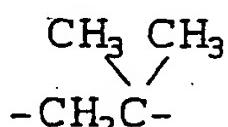
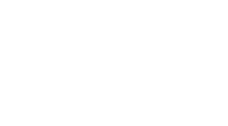
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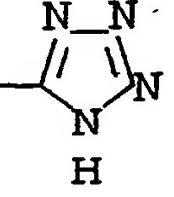
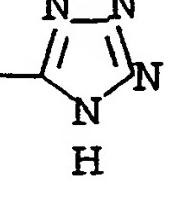
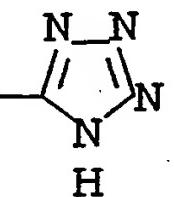
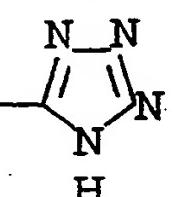
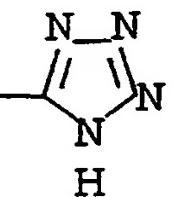
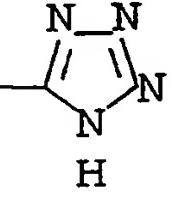
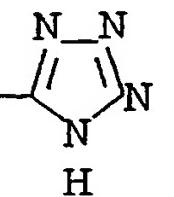
EXAMPLE E (Cont'd)

5

	X	n	p	R ^{3a}	R ⁴	A
10	-	0	3		H	
	-	0	3		$\begin{matrix} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{matrix}$	
15	-	0	1		$\begin{matrix} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{matrix}$	
	-	0	0		$\begin{matrix} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{matrix}$	
20	-	S	1		H	
25	S	1	0		$\begin{matrix} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{matrix}$	
30	S	1	0		$\begin{matrix} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{matrix}$	

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EXAMPLE E (Cont'd)

X	n	p	R ^{3a}	R ⁴	A
5	SO	1	0		-CH ₂ CH(OH)CH ₃ -CH ₂ C(CH ₃) ₂ -
10	S	1	0		H -C(CH ₃) ₂ -
15	SO	1	0		H -C(CH ₃) ₂ -
20	O	1	1		-CH ₂ CH(OH)CH ₃ -CH ₂ C(CH ₃) ₂ -
25	O	1	1		H -C(CH ₃) ₂ -
30	C=O	1	1		-CH ₂ CH(OH)CH ₃ -CH ₂ C(CH ₃) ₂ -
	CHOH	1	1		

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EXAMPLE E (Cont'd)

5

	X	n	p	R ^{3a}	R ⁴	A
10	S	1	0	-CONH ₂	$\begin{array}{c} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3 \text{ CH}_3 \\ \diagdown \quad \diagup \\ -\text{CH}_2\text{C}- \end{array}$
15	S	1	0	-CONHET	$\begin{array}{c} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3 \text{ CH}_3 \\ \diagdown \quad \diagup \\ -\text{CH}_2\text{C}- \end{array}$
	S	1	0	-CONHET	$\begin{array}{c} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_2\text{OH} \end{array}$	$\begin{array}{c} \text{CH}_3 \text{ CH}_3 \\ \diagdown \quad \diagup \\ -\text{CH}_2\text{C}- \end{array}$
20	SO	1	0	-CONHET	$\begin{array}{c} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_2\text{OH} \end{array}$	$\begin{array}{c} \text{CH}_3 \text{ CH}_3 \\ \diagdown \quad \diagup \\ -\text{CH}_2\text{C}- \end{array}$
25	S	1	0	-CONHOH	$\begin{array}{c} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3 \text{ CH}_3 \\ \diagdown \quad \diagup \\ -\text{CH}_2\text{C}- \end{array}$
	O	1	1	-CONHET	$\begin{array}{c} \text{OH} \\ \equiv \\ -\text{CH}_2\text{CHCH}_3 \end{array}$	$\begin{array}{c} \text{CH}_3 \text{ CH}_3 \\ \diagdown \quad \diagup \\ -\text{CH}_2\text{C}- \end{array}$
30						

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WHAT IS CLAIMED IS:

1. A compound having the formula:

5

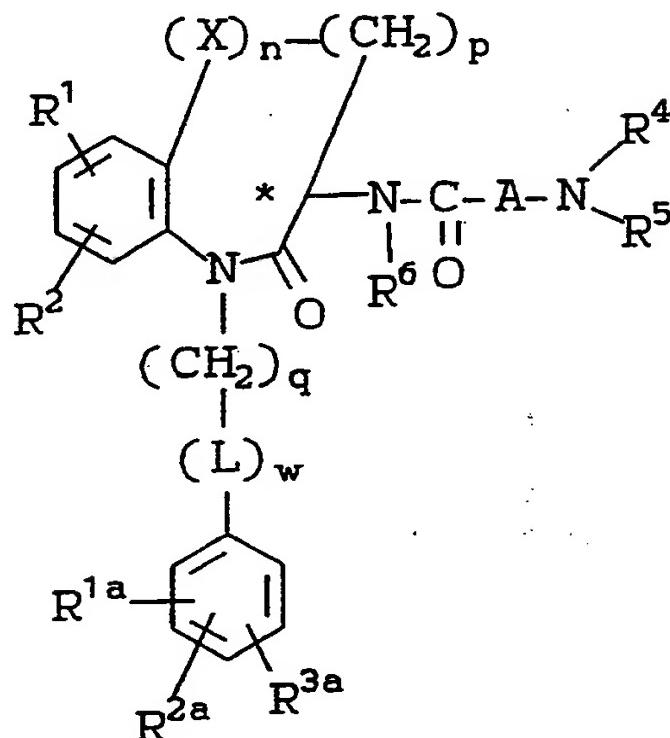
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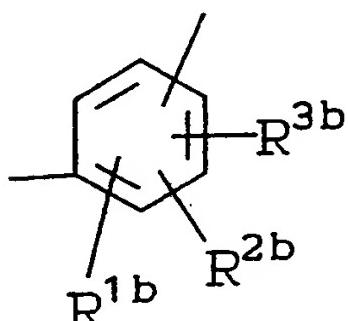
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25

30



where L is



n is 0 or 1;

p is 0 to 3;

q is 0 to 4;

w is 0 or 1;

SUBSTITUTE SHEET

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X is C=O, O, S(O)_m, -CH-, -N-, -CH=CH-;

m is 0 to 2;

5 R¹, R², R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently hydrogen, halogen, C₁-C₇ alkyl, C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy, -S(O)_mR^{7a}, cyano, nitro, R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, R^{7b}OCO(CH₂)_v, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or hydroxy;

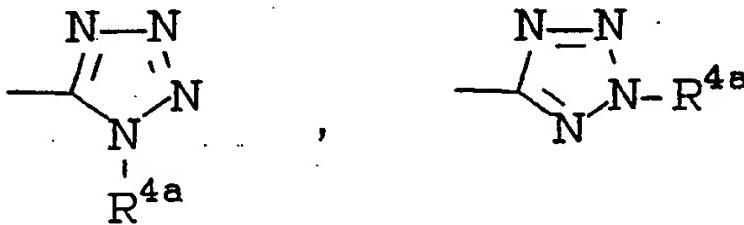
10 R^{7a} and R^{7b} are independently hydrogen, C₁-C₃ perfluoroalkyl, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, where the substituents are phenyl or substituted phenyl; phenyl or substituted phenyl where the phenyl substitutents are from 1 to 3 of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or hydroxy and v is 0 to 3;

15 R^{3a} and R^{3b} are independently hydrogen, R⁹, C₁-C₆ alkyl substituted with R⁹, phenyl substituted with R⁹ or phenoxy substituted with R⁹;

20

R⁹ is

25



30

R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, R^{7b}OCO(CH₂)_v-, R^{7b}CO(CH₂)_v-, R^{7b}O(CH₂)_vCO-, R⁴R⁵N(CH₂)_v-, R^{7b}CON(R⁴)(CH₂)_v-, R⁴R⁵NCO(CH₂)_v-, R⁴R⁵NCS(CH₂)_v-, R⁴R⁵NN(R⁵)CO(CH₂)_v-, R⁴R⁵NN(R⁵)CS(CH₂)_v-, R^{7b}CON(R⁴)N(R⁵)CO(CH₂)_v-, R^{7b}CON(R⁴)N(R⁵)CS(CH₂)_v-, R⁴N(OR^{7b})CO(CH₂)_v- or R^{7a}CON(OR^{7b})CO(CH₂)_v;

and v is as defined above;

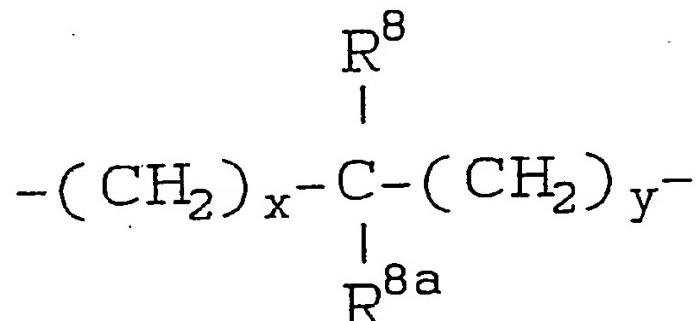
-323-

R⁴, R^{4a}, R⁵ are independently hydrogen, phenyl, substituted phenyl, C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkyl, C₃-C₁₀ alkenyl, substituted C₃-C₁₀ alkenyl, C₃-C₁₀ alkynyl, or substituted C₃-C₁₀ alkynyl where
5 the substituents on the phenyl, alkyl, alkenyl or alkynyl are from 1 to 5 of hydroxy, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, phenyl C₁-C₃ alkoxy, fluoro, R¹ substituted or R¹, R² independently disubstituted phenyl C₁-C₃ alkoxy, phenyl, R¹ substituted or R¹, R²
10 independently disubstituted phenyl, where the substituents on the phenyl are as defined above, C₁-C₅-alkanoyloxy, C₁-C₅ alkoxycarbonyl, carboxy, formyl, or -NR¹⁰R¹¹ where R¹⁰ and R¹¹ are independently hydrogen, C₁-C₆ alkyl, phenyl, phenyl
15 C₁-C₆ alkyl, C₁-C₅-alkoxycarbonyl or C₁-C₅-alkanoyl-C₁-C₆ alkyl; or R⁴ and R⁵ can be taken together to form -(CH₂)_rB(CH₂)_s- where B is CH₂, O or S(O)_m or N-R¹⁰, r and s are independently 1 to 3, and R¹⁰ is as
20 defined above;

R⁶ is hydrogen, C₁-C₁₀ alkyl, phenyl or phenyl C₁-C₁₀ alkyl;

A is

25



30

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where x and y are independently 0-3;
R⁸ and R^{8a} are independently hydrogen, C₁-C₁₀ alkyl,
trifluoromethyl, phenyl, substituted C₁-C₁₀ alkyl
where the substituents are from 1 to 3 of imidazolyl,
5 indolyl, hydroxy, fluoro, S(O)_mR^{7a}, C₁-C₆ alkoxy,
C₃-C₇ cycloalkyl, phenyl C₁-C₃ alkoxy, R¹ substituted
or R¹, R² independently disubstituted phenyl C₁-C₃
alkoxy, phenyl, R¹ substituted or R¹, R²
independently disubstituted phenyl,
10 C₁-C₅-alkanoyloxy, C₁-C₅ alkoxycarbonyl, carboxy,
formyl, or -NR¹⁰R¹¹ where R¹⁰ and R¹¹ are as defined
above; or
R⁸ and R^{8a} can be taken together to form -(CH₂)_t-
where t is 2 to 6; and R⁸ and R^{8a} can independently
15 be joined to one or both of R⁴ and R⁵ to form alkyl
bridges between the terminal nitrogen and the alkyl
portion of the A group wherein the bridge contains
from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

20

2. A compound of Claim 1 wherein:

n is 0 or 1;
p is 0 to 3;
25 q is 0 to 2;
w is 0 or 1;

R¹⁰
|
X is O, S(O)_m, -N-, -CH=CH-;
30 m is 0 to 2;
R¹, R², R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently
hydrogen, halogen, C₁-C₇ alkyl, C₁-C₃ perfluoroalkyl,

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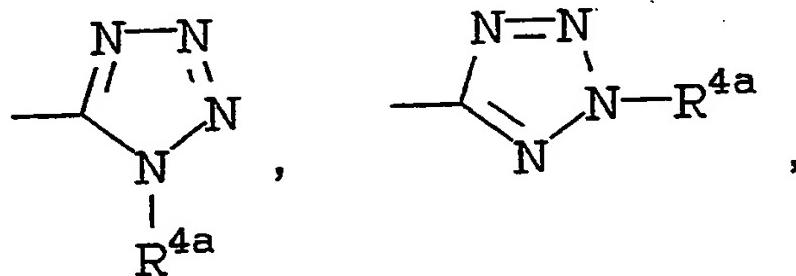
$-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v-$, $R^{7b}COO(CH_2)_v-$, $R^{7b}OCO(CH_2)_v-$, phenyl or substituted phenyl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy;

5 R^{7a} and R^{7b} are independently hydrogen, C_1-C_3 perfluoroalkyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, where the substituents are phenyl; phenyl and v is 0 to 2;

10 R^{3a} and R^{3b} are independently hydrogen, R^9 , C_1-C_6 alkyl substituted with R^9 , phenyl substituted with R^9 or phenoxy substituted with R^9 ;

R^9 is

15



20

$R^{7b}O(CH_2)_v-$, $R^{7b}COO(CH_2)_v-$, $R^{7b}OCO(CH_2)_v-$, $R^{7b}CO(CH_2)_v-$, $R^4R^5N(CH_2)_v-$, $R^{7b}CON(R^4)(CH_2)_v-$, $R^4R^5NCO(CH_2)_v-$, $R^4R^5NCS(CH_2)_v-$, $R^4R^5NN(R^5)CO(CH_2)_v-$, $R^{7b}CON(R^4)N(R^5)CO(CH_2)_v-$, $R^4N(OR^{7b})CO(CH_2)_v-$ or $R^{7a}CON(OR^{7b})CO(CH_2)_v-$; where v is as defined above;

25

R^4 , R^{4a} , R^5 are independently hydrogen, C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, where the substituents on the alkyl are from 1 to 5 of hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, phenyl C_1-C_3 alkoxy, fluoro, R^1 substituted or R^1 , R^2 independently disubstituted phenyl C_1-C_3 alkoxy, phenyl, R^1 substituted or R^1 , R^2 independently disubstituted phenyl, where the substituents on the phenyl are as defined above,

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C_1-C_5 -alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy or formyl;

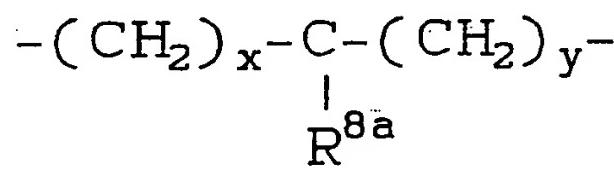
R^4 and R^5 can be taken together to form

$-(CH_2)_rB(CH_2)_s-$ where B is CH_2 , O or $S(O)_m$ or $N-R^{10}$

5 r and s are independently 1 to 3 and R^{10} is as defined above;

R^6 is hydrogen, C_1-C_{10} alkyl or phenyl C_1-C_{10} alkyl;

10 A is



where x and y are independently 0-2;

R^8 and R^{8a} are independently hydrogen, C_1-C_{10} alkyl,

20 substituted C_1-C_{10} alkyl where the substituents are from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro, $S(O)_mR^{7a}$, C_1-C_6 alkoxy, phenyl, R^1 substituted or R^1 , R^2 independently disubstituted phenyl,

25 C_1-C_5 -alkanoyloxy, C_1-C_5 alkoxycarbonyl, carboxy, formyl, $-NR^{10}R^{11}$ where R^{10} and R^{11} are independently

hydrogen, C_1-C_6 alkyl, or C_1-C_5 alkanoyl- C_1-C_6 alkyl; or R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$ where t is 2 to 4; and R^8 and R^{8a} can independently

30 be joined to one or both of R^4 and R^5 to form alkyl bridges between the terminal nitrogen and the alkyl portion of the A group wherein the

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bridge contains from 1 to 5 carbon atoms;
and pharmaceutically acceptable salts thereof.

3. A compound of Claim 2 wherein:

5

n is 0 or 1;

p is 0 to 2;

q is 0 to 2;

w is 0 or 1;

10 X is $S(O)_m$, $-CH=CH-$;

m is 0 or 1;

R^1 , R^2 , R^{1a} , R^{2a} , R^{1b} , and R^{2b} are independently
hydrogen, halogen, C_1-C_7 alkyl, C_1-C_3 perfluoroalkyl,
 $-S(O)_mR^{7a}$, $R^{7b}O(CH_2)_v-$, $R^{7b}COO(CH_2)_v-$, $R^{7b}OCO(CH_2)_v-$,

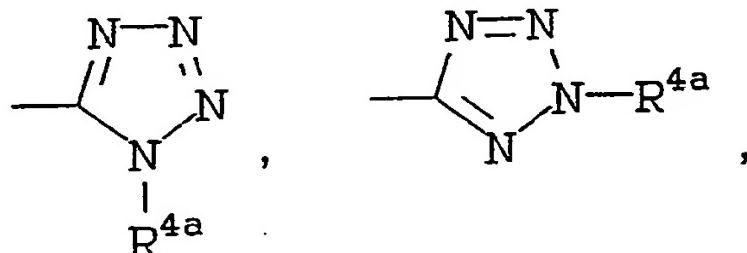
15 phenyl or substituted phenyl where the substituents
are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6
alkoxy, or hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C_1-C_6 alkyl,
substituted C_1-C_6 alkyl, where the substituents are

20 phenyl and v is 0 to 2;

R^{3a} and R^{3b} are independently hydrogen, R^9 , C_1-C_6
alkyl substituted with R^9 , phenyl substituted with R^9
or phenoxy substituted with R^9 ;

25 R^9 is

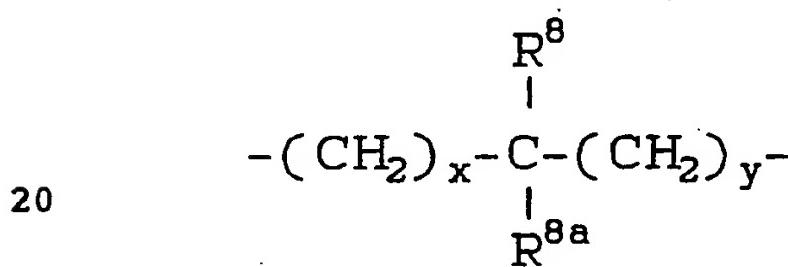


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R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, R^{7b}OCO(CH₂)_v-,
 R^{7b}CO(CH₂)_v-, R⁴R⁵N(CH₂)_v-, R^{7b}CON(R⁴)(CH₂)_v-,
 R⁴R⁵NCO(CH₂)_v-, R⁴R⁵NCS(CH₂)_v-, R⁴N(OR^{7b})CO(CH₂)_v- or
 R^{7a}CON(OR^{7b})CO(CH₂)_v-; where v is as defined above;
 5 R⁴, R^{4a}, R⁵ are independently hydrogen, C₁-C₁₀ alkyl,
 substituted C₁-C₁₀ alkyl, where the substituents on
 the alkyl, are from 1 to 5 of hydroxy, C₁-C₆ alkoxy,
 fluoro, phenyl, R¹ substituted or R¹, R²
 independently disubstituted phenyl, where the
 10 substituents on the phenyl are as defined above,
 C₁-C₅-alkanoyloxy, C₁-C₅ alkoxy carbonyl, carboxy;
 R⁶ is hydrogen, C₁-C₁₀ alkyl;

15 A is



where x and y are independently 0-2;
 R⁸ and R^{8a} are independently hydrogen, C₁-C₁₀ alkyl,
 25 substituted C₁-C₁₀ alkyl where the substituents are
 from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro,
 S(O)_mR^{7a}, C₁-C₆ alkoxy, phenyl, R¹ substituted or R¹,
 R² independently disubstituted phenyl,
 C₁-C₅-alkanoyloxy, C₁-C₅ alkoxy carbonyl, carboxy; or
 30 R⁸ and R^{8a} can be taken together to form -(CH₂)_t-
 where t is 2; and R⁸ and R^{8a} can

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independently be joined to one or both of R⁴ and R⁵
 to form alkyl bridges between the terminal nitrogen
 and the alkyl portion of the A group wherein the
 bridge contains from 1 to 5 carbon atoms;
 5 and pharmaceutically acceptable salts thereof.

4. A compound of Claim 3 wherein:

n is 0 or 1;

10 p is 0 to 2;

q is 1;

w is 1;

X is S(0)_m or -CH=CH-;

m is 0 or 1;

15 R¹, R², R^{1a}, R^{2a}, R^{1b}, and R^{2b} are independently
 hydrogen, halogen, C₁-C₇ alkyl, C₁-C₃ perfluoroalkyl,
 -S(0)_mR^{7a}, R^{7b}O(CH₂)_v-, R^{7b}COO(CH₂)_v-, phenyl or
 substituted phenyl where the substituents are from 1
 to 3 of halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, or

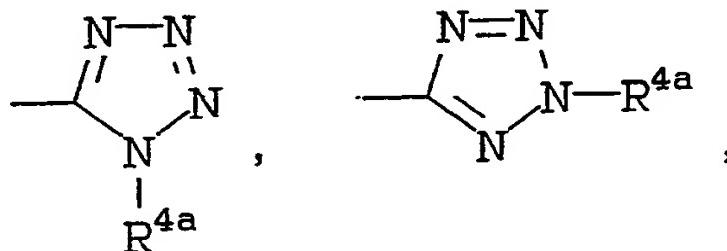
20 hydroxy;

R^{7a} and R^{7b} are independently hydrogen, C₁-C₆ alkyl,
 substituted C₁-C₆ alkyl, where the substituents are
 phenyl, phenyl and v is 0 to 1;

R^{3a} and R^{3b} are independently hydrogen or R⁹;

25

R⁹ is



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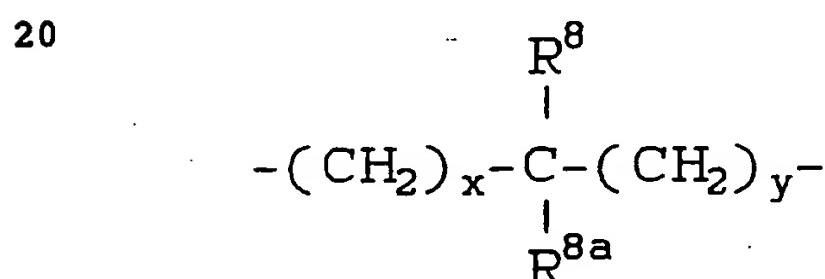
$R^{7b}O(CH_2)_v^-$, $R^{7b}COO(CH_2)_v^-$, $R^{7b}OCO(CH_2)_v^-$,
 $R^{7b}CO(CH_2)_v^-$, $R^4R^5N(CH_2)_v^-$, $R^{7b}CON(R^4)(CH_2)_v^-$,
 $R^4R^5NCO(CH_2)_v^-$ or $R^4N(OR^{7b})CO(CH_2)_v^-$; where v is as
defined above;

5 R^4 , R^5 are independently hydrogen, C₁-C₁₀ alkyl,
substituted C₁-C₁₀ alkyl, where the substituents on
the alkyl are from 1 to 3 of hydroxy, C₁-C₃ alkoxy,
fluoro, phenyl, R¹ substituted or R¹, R²
independently disubstituted phenyl, where the
10 substituents on the phenyl are as defined above;

15 R^{4a} is hydrogen, C₁-C₁₀ alkyl, substituted C₁-C₁₀
alkyl where the substituents on the alkyl are from 1
to 3 of hydroxy.

15 R^6 is hydrogen;

A is

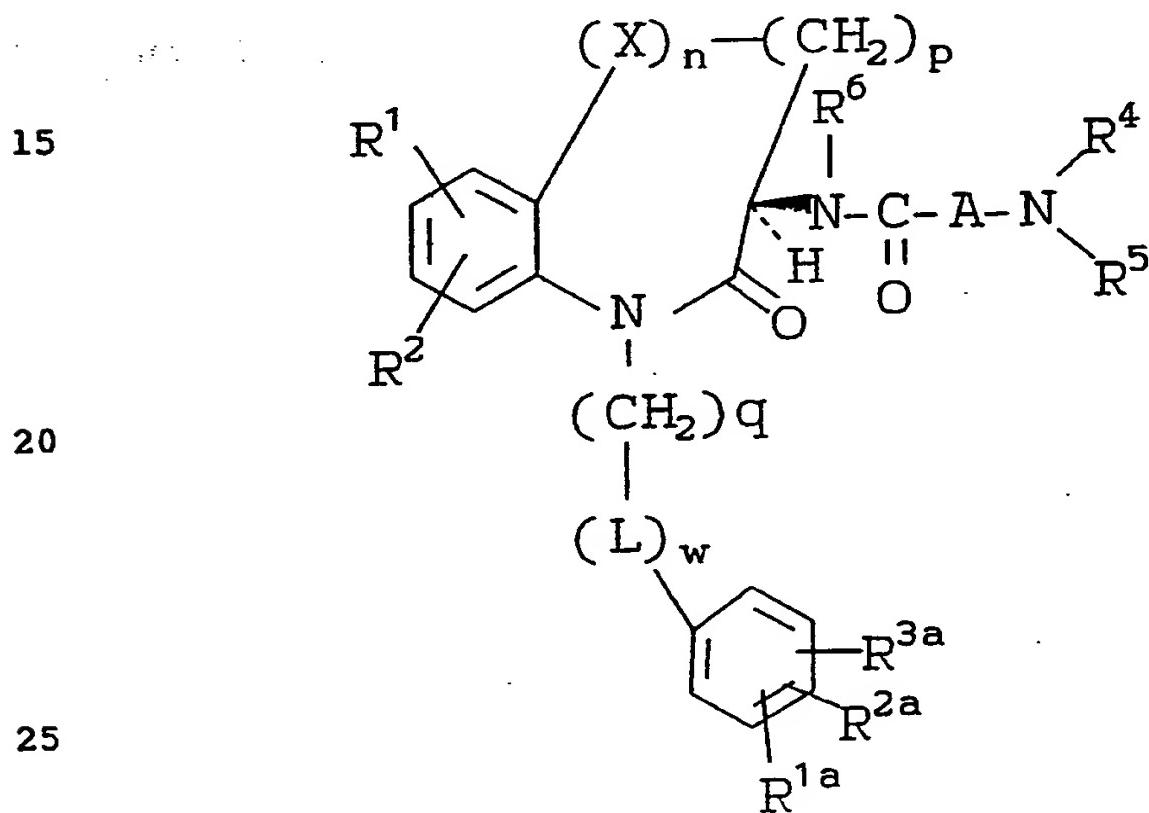


25 where x and y are independently 0-1;
 R^8 and R^{8a} are independently hydrogen, C₁-C₁₀ alkyl,
substituted C₁-C₁₀ alkyl where the substituents are
from 1 to 3 of imidazolyl, indolyl, hydroxy, fluoro,
30 S(O)_mR^{7a}, C₁-C₆ alkoxy, phenyl, R¹ substituted or R¹,
R² independently disubstituted phenyl,

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C_1-C_5 -alkanoyloxy, C_1-C_5 alkoxy carbonyl, carboxy; or
 R^8 and R^{8a} can be taken together to form $-(CH_2)_t-$
 where t is 2; and R^8 and R^{8a} can independently be
 joined to one or both of R^4 and R^5 to form alkyl
 5 bridges between the terminal nitrogen and the alkyl
 portion of the A group wherein the bridge contains
 from 1 to 5 carbon atoms;
 and pharmaceutically acceptable salts thereof.

10 5. A stereospecific compound of Claim 1
 having the following structural formula:



where R^1 , R^2 , X , n , p , q , L , w , R^{1a} , R^{2a} , R^{3a} , R^4 ,
 R^5 , A and R^6 are as defined in Claim 1

30

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6. A compound of Claim 1 which is:

- 5 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-butanamide;
- 10 2(R)-amino-3-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-
1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-propanamide;
- 15 2(R)-amino-3-phenyl-N-[2,3,4,5-tetrahydro-2-oxo-
1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-propanamide;
- 20 2(R)-amino-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-
(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-
1-benzazepin-3(R)-yl]-propanamide;
- 25 3-(2-hydroxyethyl)amino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1-(2-hydroxyethyl)-
tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-
1-benzazepin-3(R)-yl]-butanamide;
- 30 3-(2-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-
butanamide;
- 2-amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]-
methyl]-1H-1-benzazepin-3(R)-yl]-propanamide;

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3-amino-3-methyl-N-[7-fluoro-2,3,4,5-tetrahydro-
2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide;

5 3-amino-3-methyl-N-[7-trifluoromethyl-2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-y1]-
butanamide;

10 3-amino-3-methyl-N-[6-fluoro-2,3,4,5-tetrahydro-
2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3(R)-y1]-butanamide;

15 3-benzylamino-3-methyl-N-[2,3,4,5-tetrahydro-2-
oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]-methyl]-1H-1-benzazepin-3(R)-y1]-butanamide;
or

20 3-amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2'-(1H-
tetrazol-5-yl)[1,1'-biphenyl]-4-y1]methyl]-1,5-
benzothiazepin-3(S)-y1]-butanamide;

25 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-y1]-
butanamide

30 3-(2(S)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-y1]methyl]-1H-1-benzazepin-3(R)-y1]-
butanamide

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3-(2(R),3-dihydroxypropyl)amino-3-methyl-N-[2,3,-
4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-
[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3(R)-yl]-butanamide

5

3-(2(S),3-dihydroxypropyl)amino-3-methyl-N-[2,3,-
4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-
[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-
yl]-butanamide

10

3-(3(S)-hydroxybutyl)amino-3-methyl-N-[7-fluoro-
2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-
yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3(R)-yl]-butanamide

15

3-(3(S)-hydroxybutyl)amino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-
butanamide

20

3-amino-3-methyl-N-[7-hydroxy-2,3,4,5-tetrahydro-
2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

25

3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-hydroxy-
2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-
yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3(R)-yl]-butanamide

30

3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-fluoro-
2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-
yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-
3(R)-yl]-butanamide

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2-(3(R)-hydroxybutyl)amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

5

2-(3(S)-hydroxybutyl)amino-2-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-propanamide

10

3-Amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

15

3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

20

3-(3(S)-hydroxybutyl)amino-3-methyl-N-[7-methoxy-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide

25

Quinuclidine-N'-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-3-carboxamide

30

3-(2-fluoropropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

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3-(2-methoxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

5

3-(2-hydroxy-2-methylpropyl)amino-3-methyl-N-[2,-3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]butanamide

10

4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-2,-3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-methyl]-[1,1'-biphenyl]-2-carboxamide

15

4'-[[3(R)-[[3-[(2(R)-hydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide

20

4'-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide

25

N-ethyl-4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)-amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide

30

N-ethyl-4'-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide

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N-methyl-4'-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-
amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-
hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-
biphenyl]-2-carboxamide

5

3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-hydroxymethyl[1,1'-biphenyl]-4-yl]methyl]-1H-
1-benzazepin-3(R)-yl]butanamide

10

3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-
tetrahydro-2-oxo-1-[[2'-hydroxymethyl[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-
butanamide

15

3-Amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-
[[2'-aminomethyl[1,1'-biphenyl]-4-yl]methyl]-1H-1-
benzazepin-3(R)-yl]butanamide

20

3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,-
5-tetrahydro-2-oxo-1-[[2'-aminomethyl[1,1'-
biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-
butanamide

25

4'-[[3(R)-[[3-[(2(S),3(S),4-trihydroxybutyl)-
amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-
hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-
biphenyl]-2-carboxamide

30

4'-[[3(R)-[[3-[(3-hydroxybutyl)amino]-3-methyl-1-
oxobutyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-ben-
zazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide

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3-Amino-3-methyl-N-[2,3-dihydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]butanamide

- 5 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3-dihydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide
- 10 N-ethyl-4'-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino]-2,3-dihydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-biphenyl]-2-carboxamide
- 15 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide
- 20 3-(2(S)-hydroxypropyl)amino-3-methyl-N-[3,4-dihydro-4-oxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-yl]-butanamide
- 25 N-ethyl-4'-[[3(S)-[[3-[(2(S),3-dihydroxypropyl)-amino]-3-methyl-1-oxobutyl]amino]-3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2H)-yl]methyl]-[1,1'-biphenyl]-2-carboxamide
- 30 4'-[[3(S)-[(3-amino-3-methyl-1-oxobutyl)amino]-3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2H)-yl]-methyl]-[1,1'-biphenyl]-2-carboxamide

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4'-[[3(R)-[(3-amino-3-methyl-1-oxobutyl)amino]-
2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepin-1-yl]-
methyl]-[1,1'-biphenyl]-2-thioamide

5 N-hydroxy-4'-[[3(R)-[(3-amino-3-methyl-1-oxobut-
y1)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benz-
azepin-1-yl]-methyl]-[1,1'-biphenyl]-2-carboxamide

10 N-hydroxy-4'-[[3(R)-[[3-[(2(S),3-dihydroxypropyl)-
amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-
hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-bi-
phenyl]-2-carboxamide

15 N-hydroxy-4'-[[3(R)-[[3-[(2(R)-hydroxypropyl)-
amino]-3-methyl-1-oxobutyl]amino]-2,3,4,5-tetra-
hydro-2-oxo-1H-1-benzazepin-1-yl]methyl]-[1,1'-
biphenyl]-2-carboxamide

20 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[3,4-di-
hydro-1,4-dioxo-5-[[2'-(1H-tetrazol-5-yl)[1,1'-
biphenyl]-4-yl]methyl]-1,5-benzothiazepin-3(S)-
y1]-butanamide

25 3-amino-3-methyl-N-[3,4-dihydro-1,4-dioxo-5-[[2'-(
1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
1,5-benzothiazepin-3(S)-y1]-butanamide

30 3-amino-3-methyl-N-[7-methylthio-2,3,4,5-tetra-
hydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-bi-
phenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-y1]buta-
namide

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3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methyl-thio-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

5

3-(2(R)-hydroxypropyl)amino-3-methyl-N-[7-methyl-sulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

10

3-amino-3-methyl-N-[7-methylsulfinyl-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

15

3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(acetylaminomethyl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]butanamide

20

3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(acetylaminomethyl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

25

3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(benzoylaminomethyl)[1,1'-biphenyl]-4-yl]-methyl]-1H-1-benzazepin-3(R)-yl]butanamide

30

3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(benzoylaminomethyl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepin-3(R)-yl]-butanamide

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3-amino-3-methyl-4-hydroxy-N-[2,3,4,5-tetrahydro-
2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]-methyl]-1H-1-benzazepin-3(R)-yl]butanamide

5

2-Amino-2-methyl-3-hydroxy-N-[2,3,4,5-tetrahydro-
2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-
y1]methyl]-1H-1-benzazepin-3(R)-yl]propanamide

10

3-(2(R)-hydroxypropyl)amino-3-methyl-4-hydroxy-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-
y1)[1,1'-biphenyl]-4-y1]methyl]-1H-1-benzazepin-3-
(R)-yl]-butanamide

15

2-(3-hydroxybutyl)amino-2-methyl-3-hydroxy-N-[2,-
3,4,5-tetrahydro-2-oxol-[[2'-(1H-tetrazol-5-yl)-
[1,1'-biphenyl]-4-y1]methyl]1H-1-benzazepin-3(R)-
y1]propanamide

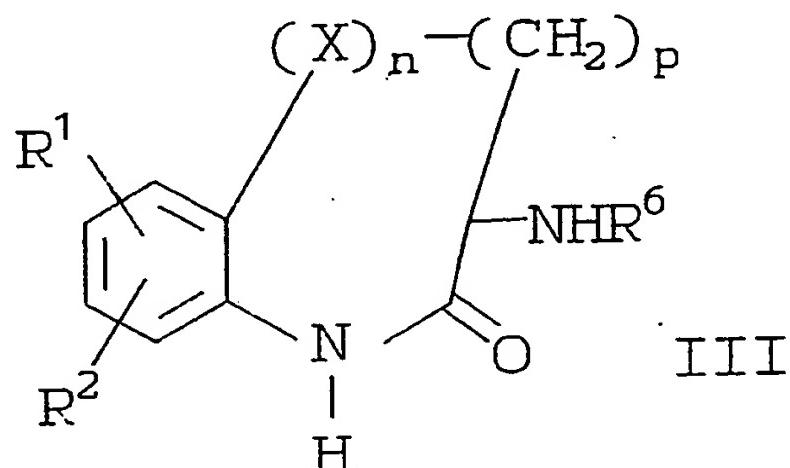
20

and pharmaceutically acceptable salts of such
compounds.

25

7. A process for the preparation of a
compound of Claim 1 which comprises reacting a
compound having a formula:

30

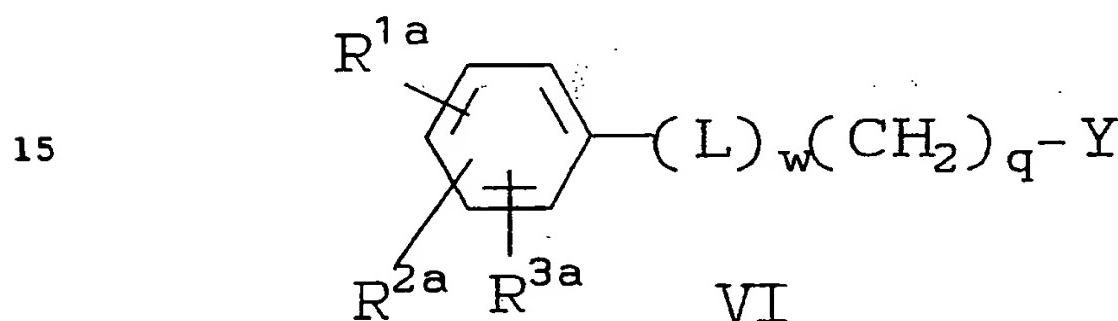


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where R^1 , R^2 , R^6 , X, n and p are as defined in Claim 1 with a compound having the formula:



where R⁵ and A are as defined in Claim 1 and G is a protecting group; which step is either followed by or preceded by the treatment of the compound with

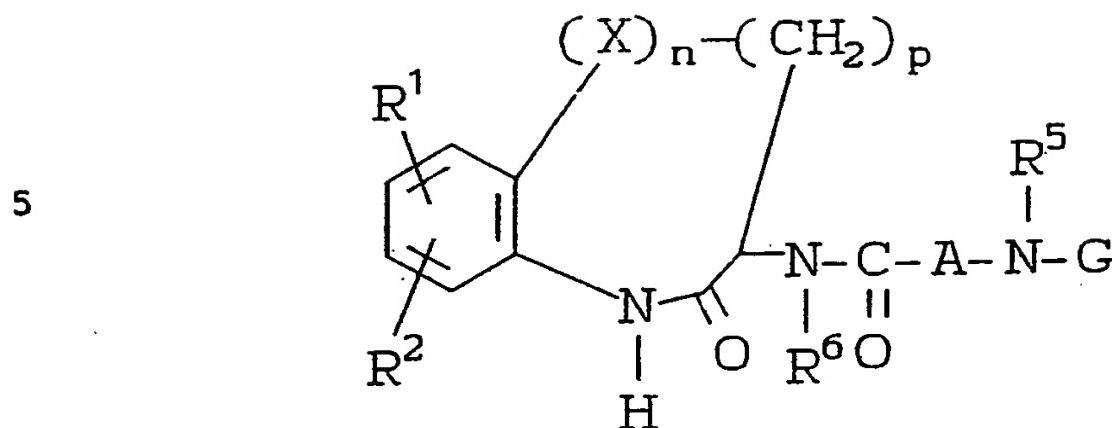


20 where R^{1a} , R^{2a} , R^{3a} , L, w and q are as defined in
 Claim 1 and Y is a leaving group, followed by the
 replacement of the protecting group with R^4 .

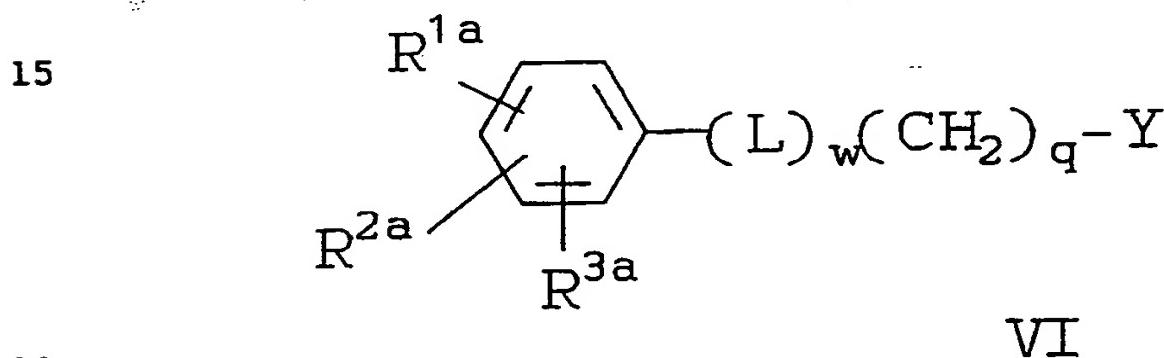
25 8. The process of Claim 7 where compound
III is first reacted with compound IV followed by
reaction with compound VI.

30 9. A process for the preparation of a compound of Claim 1 which comprises reacting a compound having a formula:

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10 where R¹, R², R⁵, R⁶, X, n and p are as defined in Claim 1 and G is a protecting group, with a compound having the formula:



20

where R¹a, R²a, R³a, L, w and q are as defined in Claim 1 and Y is a leaving group, followed by replacement of the protecting group G with R⁴.

25

10. The process of Claim 9 where the protecting group G is t-butoxycarbonyl or benzyloxycarbonyl and L is chlorine, bromine, iodine, O-methanesulfonyl or O-(p-toluenesulfonyl).

30

11. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of a compound of Claim 1.

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12. A composition useful for increasing the
endogenous production or release of growth hormone in
a human or an animal which comprises an inert carrier
5 and an effective amount of a compound of Claim 1.

13. A composition useful for increasing the
endogenous production/release of growth hormone in a
human or an animal which comprises an inert carrier
10 and an effective amount of a compound of Claim I used
in combination with other growth hormone
secretagogues such as, GHRP-6 or GHRP-1, growth
hormone releasing factor (GRF) or one of its analogs,
IGF-1 or IGF-2, or B-HT920.
15

20

25

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/02271

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1. 5 C07D403/10;	C07D223/16;	C07D401/10;	C07D417/10
C07D227/10;	C07K5/06;	C07D281/10;	A61K31/33

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.C1. 5	C07D ; C07K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 349 949 (FUJISAWA) 10.January 1990 see page 49 - page 53; claims ----	1-13
A	EP,A,0 166 357 (MERCK) 2 January 1986 see page 54 - page 59; claims ----	1-13
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 32, no. 8, August 1989, WASHINGTON pages 1681 - 1685; PARSONS W. H.: 'Cholecystokinin Antagonists. Synthesis and biological evaluation of 3-substituted benzolactams.' ----	1-13

¹⁰ Special categories of cited documents :¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

¹¹ T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention¹² X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step¹³ Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art¹⁴ A document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

2

05 AUGUST 1992

Date of Mailing of this International Search Report

14.08.92

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

LUYTEN H.W.



**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9202271
SA 59195**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 05/08/92

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0349949	10-01-90	AU-A-	3785989	11-01-90
		CN-A-	1041941	09-05-90
		JP-A-	2056481	26-02-90
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EP-A-0166357	02-01-86	JP-A-	61015875	23-01-86
		US-A-	4692522	08-09-87
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